MICARDIS® (TELMISARTAN) TABLETS

ACADEMY OF MANAGED CARE PHARMACY (AMCP)

FORMULARY DOSSIER

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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DRUG INFORMATION UNIT
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ACADEMY OF MANAGED CARE PHARMACY DOSSIER

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I. INTRODUCTION

The purpose of this formulary submission dossier is to present the clinical and economic rationale to support the acceptance and use of MICARDIS® (telmisartan) for the management of hypertension. MICARDIS is an angiotensin type II receptor antagonist that provides 24-hour control of blood pressure (BP) from a once-daily dose. This dossier presents the ways in which MICARDIS will add value to the current management of hypertension, both in terms of clinical effectiveness and economic efficiency.

I.1 Structure of This Dossier

Section II provides a description of MICARDIS (including a cross-label comparison with its main competitors, Cozaar® and Diovan®), hypertension, and its management.

Section III provides a summary of the supporting clinical and pharmacoeconomic evidence for MICARDIS based on results from pivotal efficacy studies.

Section IV provides a discussion of the expected economic impact of MICARDIS on patient management and a health plan's budget once it is added to the formulary, including a detailed description of the additional benefits it provides in relation to its competitor.

Section V provides a description of clinical and economic value of MICARDIS.

II. PRODUCT INFORMATION

II.1 Product Description

Generic name:	telmisartan
Brand name:	MICARDIS
Therapeutic class:	Nonpeptide angiotensin II receptor antagonist
DPS/AHFS Drug Classification:	Anti-hypertensive agent
Approval date:	November 1998

The chemical name of MICARDIS is 4-[(1,4-dimethyl-2-propyl[2,6-bi-1H-benzimidazol]-1-yl)methyl]-[1,1-biphenyl]-2-carboxylic acid.

Approved Indications
MICARDIS is indicated for the treatment of hypertension (HTN) and may be used alone or in combination with other antihypertensive agents.

Unapproved Indications
Although telmisartan is indicated for the treatment of HTN, several additional, off-label uses of the medication are under investigation. Initial studies of telmisartan therapy in patients with congestive heart failure (CHF) have been completed recently. Additional studies evaluating the use of telmisartan in patients with diabetes are in progress. Another study was recently initiated to investigate the capacity of telmisartan to further reduce the risk of recurrent stroke on top of standard treatments in both hypertensive and non hypertensive patients.

How Supplied
MICARDIS uncoated tablets contain 20, 40, or 80 mg of telmisartan.

How Supplied	NDC	AWP
Blister card, 4x7 tablets, 20 mg	00597-0039-28	$38.20
Blister card, 4x7 tablets, 40 mg	00597-0040-28	$38.20
Blister card, 4x7 tablets, 80 mg	00597-0041-28	$40.06

Dosage and Administration
Dosage must be individualized. The usual starting dose of MICARDIS tablets is 40 mg once a day. Blood pressure response is dose related over the range of 20 – 80 mg. Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional BP reduction beyond that achieved with 80 mg MICARDIS is required, a patient may be switched to MICARDIS HCT, telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary. No initial dosing adjustment is necessary for elderly patients or patients with mild-to-moderate renal impairment. Patients on dialysis may develop orthostatic hypotension; their BP should be closely monitored. MICARDIS tablets may be administered with other antihypertensive agents. MICARDIS may be taken with or without food.

Cross-Label Comparison of MICARDIS and Main Comparators

The main comparators for MICARDIS are Diovan® (valsartan) and Cozaar® (losartan potassium tablets); all of these angiotensin II antagonists act on the AT_1 receptor subtype. The product information documents for MICARDIS, Diovan® and Cozaar® are summarized in Table 1.

Table 1. Cross-Label Comparisons of Product Information for Products in Same Therapeutic Class

	MICARDIS (telmisartan)	**DIOVAN® (valsartan)**	**COZAAR® (losartan potassium tablets)**
Empirical formula	$C_{33}H_{30}N_4O_2$	$C_{24}H_{29}N_5O_3$	$C_{22}H_{22}ClKN_6O$
Molecular weight	514.63	435.50	461.01
Available formulations and indicated strengths	Tablets contain 20 mg, 40 mg, or 80 mg of telmisartan	Tablets contain 80 mg, 160 mg or 320 mg of valsartan	25 mg, 50 mg or 100 mg tablets contain 2.12 mg, 4.24 mg and 8.48 mg potassium, respectively
Indications	For the treatment of HTN; may be used alone or in combination with other antihypertensive agents	For the treatment of HTN; may be used alone or in combination with other antihypertensive agents; congestive heart failure in the ACE-intolerant patient population	For the treatment of HTN; may be used alone or in combination with other antihypertensive agents; reduce the rate of nephropathy in hypertensive type 2 diabetics with an elevated serum creatinine and proteinuria; reduce risk of stroke in hypertensives with LVH.
Clinical Pharmacology			
Mechanism of action	Blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues	Blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues	Blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues
Pharmacokinetics			
Absorption	Peak concentrations are reached in 0.5-1 hour after dosing	Peak concentrations are reached 2-4 hours after dosing	Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively
Food Effects	Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose	Food decreases the AUC by about 40% and peak plasma concentration (C_{max}) by about 50%	Food slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased)
Metabolism	Metabolized by conjugation to form a pharmacologically inactive acylglucuronide	Enzymes responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes	Undergoes substantial first-pass metabolism by cytochrome P450 enzymes; converted in part, to an active carboxylic acid metabolite
Half-life	Shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours	Shows bi-exponential decay kinetics following IV administration, with an average elimination half-life of about 6 hours	Terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours
Volume of distribution	Highly bound to plasma proteins (>99.5%), mainly albumin and α_1-	Highly bound to serum proteins (95%), mainly serum albumin;	Both losartan and its active metabolite are highly bound to

	MICARDIS (telmisartan)	**DIOVAN® (valsartan)**	**COZAAR® (losartan potassium tablets)**
	acid glycoprotein; plasma binding is constant over the concentration range achieved with recommended dose; volume of distribution is approximately 500 liters, indicating additional tissue binding	does not distribute into tissues extensively	plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively; plasma protein binding is constant over the concentration range achieved with recommended doses
Excretion	Following either IV or oral administration, most (>97%) was eliminated unchanged in feces via biliary excretion; only minute amount found in urine (0.91% and 0.49% of total radioactivity, respectively)	Following administration of oral solution, recovered primarily in feces and urine, 83% and 13% of dose, respectively; only about 20% of dose recovered as metabolites; following IV administration, plasma clearance is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance)	Following oral administration, about 35% is recovered in the urine and about 60% in the feces; following IV administration, about 45% is recovered in the urine and 50% in the feces; total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively; when losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite; biliary excretion contributes to the elimination of losartan and its metabolites
Special populations	• Not investigated in patients <18 years of age • Pharmacokinetics do not differ between elderly and those younger than 65 years • Plasma concentrations are generally 2-3 times higher in females than in males; no significant increases in BP response or in incident or orthostatic hypotension found in women • Renal excretion does not contribute to the clearance of telmisartan • In patients with hepatic insufficiency, plasma concentrations are increased, and absolute bioavailability approaches 100%	• Not investigated in patients <18 years of age • Exposure (AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young • Does not differ significantly between males and females • No apparent correlation between renal function and exposure to valsartan in patients with different degrees of renal impairment • No studies performed in patients with severe impairment of renal function • Patients with mild-to-moderate chronic liver disease have twice the exposure (AUC) to valsartan of healthy volunteers	• Not investigated in patients <18 years of age • Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives • Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females • Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min; in patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients • Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients • Following oral administration in patients with mild-to-moderate

	MICARDIS (telmisartan)	**DIOVAN® (valsartan)**	**COZAAR® (losartan potassium tablets)**
			alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers • In patients with hepatic insufficiency, total plasma clearance of losartan was about 50% lower and the oral bioavailability was about 2-times higher when compared to normal subjects
Contraindications	Contraindicated in patients who are hypersensitive to any component of this product	Contraindicated in patients who are hypersensitive to any component of this product	Contraindicated in patients who are hypersensitive to any component of this product
Warnings			
	• When pregnancy is detected, tablets should be discontinued as soon as possible • In patients with an activated renin-angiotensin system, symptomatic hypotension may occur after initiation of therapy	• When pregnancy is detected, tablets should be discontinued as soon as possible • In patients with an activated renin-angiotensin system, symptomatic hypotension may occur after initiation of therapy	• When pregnancy is detected, tablets should be discontinued as soon as possible • In patients who are intravasculary volume-depleted, symptomatic hypotension may occur after initiation of therapy
Precautions			
General	• Patients with impaired hepatic function can be expected to have reduced clearance • For patients with impaired renal function, changes in renal function may be anticipated in susceptible individuals; in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and with acute renal failure and/or death; similar results may be anticipated in patients treated with telmisartan • There has been no long term use of telmisartan tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors (increases in serum	• For patients with impaired renal function, changes in renal function may be anticipated in susceptible individuals; in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and with acute renal failure and/or death; similar results may be anticipated in patients treated with valsartan • In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or BUN were observed; there has been no long term use of valsartan tablets in patients with unilateral or bilateral renal artery stenosis, but an effect similar to	• For patients with impaired renal function, changes in renal function may be anticipated in susceptible individuals; in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and with acute renal failure and/or death; similar results may be anticipated in patients treated with losartan tablets • Angioedema including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported (rarely) • A patient receiving losartan should be told not to use potassium supplements or salt

	MICARDIS (telmisartan)	**DIOVAN® (valsartan)**	**COZAAR® (losartan potassium tablets)**
	creatinine or blood urea nitrogen [BUN]) should be anticipated Should be used with caution in patients with: • biliary obstructive disorders or hepatic insufficiency	that seen with ACE inhibitors (increases in serum creatinine or BUN nitrogen) should be anticipated Should be used with caution in patients with: • Biliary obstructive disorders or mild-to-moderate hepatic impairment • Patients with an activated renin-angiotensin system	substitutes containing potassium without consulting the prescribing physician • In patients with unilateral or biliary renal artery stenosis, effects similar to increases in serum creatinine or BUN have been reported Should be used with caution in patients with: • Impaired liver function (lower dose should be considered)
Information to patients	Female patients of childbearing age: • should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system • should be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester • should be asked to report pregnancies to their physicians as soon as possible	Female patients of childbearing age: • should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system • should be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester • should be asked to report pregnancies to their physicians as soon as possible	Female patients of childbearing age: • should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system • should be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester • should be asked to report pregnancies to their physicians as soon as possible Do not use potassium or salt substitutes containing potassium without consulting physician
Laboratory tests	Clinically relevant changes in standard laboratory test parameters were rarely associated with administration A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo A 0.5 mg/cL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo	Clinically important changes in standard laboratory parameters were rarely associated with administration Minor elevations in creatinine occurred in 0.8% of valsartan patients and 0.6% given placebo Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of valsartan patients, compared with 0.1% and 0.1% in placebo Occasional elevations (>150%) of liver chemistries occurred in valsartan patients Neutropenia was observed in 1.9%	Clinically important changes in standard laboratory parameters were rarely associated with administration Minor increases in blood urea nitrogen or serum creatinine were observed in less than 0.1% of patients with essential HTN treated with losartan alone Small decreases in hemoglobin and hematocrit occurred frequently in patients treated with losartan alone, but were rarely of clinical importance Occasional elevations of liver enzymes and/or serum bilirubin have occurred

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		of valsartan patients and 0.8% of patients treated with placebo Greater than 20% increases in serum potassium were observed in 4.4% of valsartan patients compared to 2.9% of placebo	
Carcinogenesis	No evidence of carcinogenicity when administered to mice and rats for up to 2 years at highest doses of about 59 and 13 times, respectively, the maximum recommended human dose (MRHD)	No evidence of carcinogenicity when administered to mice and rats for up to 2 years at highest doses of about 2.6 and 6 times, respective, the MRHD	Not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively; doses for losartan and its pharmacologically active metabolite were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day
Mutagenesis	No evidence of mutagenicity	No evidence of mutagenicity	No evidence of mutagenicity
Fertility impairment	No impairment of reproductive performance of male and female rats at doses 13-fold the MHRD	No adverse effects on the reproductive performance of male or female rats at doses 6-fold the MRHD	Fertility and reproductive performance were not affected in studies with males rats given oral doses up to approximately 150 mg/kg/day; administration of toxic dosages in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section; at 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed; in nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the MHRD
Pregnancy category	C (first trimester); D (second and third trimester)	C (first trimester); D (second and third trimester)	C (first trimester); D (second and third trimester)
Adverse Reactions			
Safety experience	Evaluated in more than 3,700 patients, including 1,900 treated for over six months and more than 1,300 for over one year Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy	Evaluated in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over one year Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy; overall incidence of adverse experiences	Evaluated in more than 3,300 patients treated for essential HTN and 4,058 patients/subjects overall; over 1,200 patients were treated for over six months and more than 800 for over one year Treatment was well-tolerated; overall incidence of adverse experiences reported with losartan similar to placebo

	MICARDIS (telmisartan)	**DIOVAN® (valsartan)**	**COZAAR® (losartan potassium tablets)**
		with valsartan similar to placebo	
Adverse events	Adverse events (in placebo-controlled trials) where frequency was ≥1% in telmisartan patients receiving 20-160 mg monotherapy for up to 12 weeks (n=1,455) and rate > placebo group (n=380): • Upper respiratory tract infection (7% vs. 6% placebo) • Back pain (3% vs. 1% placebo) • Sinusitis (3% vs. 2% placebo) • Diarrhea (3% vs. 2% placebo) • Pharyngitis (1% vs. 0% placebo)	Adverse events (in placebo-controlled trials) where frequency was ≥1% in valsartan patients (n=2,316) and rate > placebo group (n=888): • Viral infection (3% vs. 2% placebo) • Fatigue (2% vs. 1% placebo) • Abdominal pain (2% vs. 1% placebo)	Adverse events (in four 6-12 week placebo-controlled trials) where frequency was ≥1% in losartan patients receiving 10-150 mg (n=1,075) and rate > placebo group (n=334): • Diarrhea (2.4% vs. 2.1%) • Dyspepsia (1.3% vs. 1.2%) • Muscle cramp (1.1% vs. 0.3%) • Myalgia (1.0% vs. 0.9%) • Back pain (1.8% vs. 1.2%) • Pain, leg (1.0% vs. 0.0%) • Dizziness (3.5% vs. 2.1%) • Insomnia (1.4% vs. 0.6%) • Nasal congestion (2.0% vs. 1.2%) • Cough (3.4% vs. 3.3%) • Upper respiratory infection (7.9% vs. 6.9%) • Sinus disorder (1.5% vs. 1.2%) • Sinusitis (1.0% vs. 0.3%)
Drug/Drug Interactions	• When co-administered with digoxin, it is recommended that digoxin levels be monitored with initiating, adjusting, and discontinuing telmisartan • Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, hydrochlorothiazide or ibuprofen • Not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19; *in vitro*, has some inhibition of CYP2C19	• The inhibitory or induction potential of valsartan on CYP 450 is unknown • No clinically significant interactions were observed when co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin • Administration with warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin	• An inhibitor of P450 3A4 did not affect the conversion of losartan to the active metabolite after IV administration of losartan • No significant interactions found with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital

II.2 Place of product in therapy

II.2.a Disease description

The Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has published its sixth report in which normal to high BP values are classified for adults over the age of 18 (JNC-VI, 1997). Hypertension is defined in adults as a SBP of ≥ 140 mm Hg or a DBP of ≥ 90 mm Hg. The disease can be separated into two types: primary HTN, in which the cause is unknown and secondary HTN which is the result of an underlying condition (i.e., renal abnormalities, structural abnormalities in the aorta, or a narrowing of other coronary arteries). Approximately 90-95% of all cases are classified as primary HTN (JNC-VI, 1997). As the prevalence of this illness increases, the level of use of health care resources for the treatment of HTN also increases. Total (direct and indirect) costs associated with HTN are estimated to be $40.4 billion (2001 US $) in the US (AHA, 2001). Prescriptions represent the largest component of direct costs (41%). Indirect costs (lost productivity due to morbidity and mortality of HTN) add $10.8 billion.

II.2.b Epidemiology and risk factors

A recent survey shows that approximately 50 million Americans (six years of age and older) suffer from high BP, which translates into a national prevalence rate of 20% (NHANES III, 1997). Among adults (aged 18 and older), nearly 25% of individuals suffer from the disease (AHA, 2001). Because of the asymptomatic nature of HTN, roughly 31.6% of those who have the condition are unaware of it (AHA, 2001). In 1998, HTN was listed as the primary cause of death for 44,435 persons in the United States. This figure reflects a mortality rate that is up 16.0% from 1998 (AHA, 2001). Furthermore, the condition resulted in the deaths of an additional 210,000 people through its association with different cardiovascular co-morbidities. An increased awareness of the disease and improvement in the ability to detect HTN, may be responsible for the growth in the prevalence of HTN since 1988.

Multiple risk factors contribute to HTN; these factors are either uncontrollable (e.g. race, family history, and age) or controllable (e.g. lifestyle habits). Prevalence rates among Hispanics and American Indians are equal to those seen in the Caucasian population, while African-Americans show significantly higher rates of HTN. Recent results show death rates from high BP to be 13.9 (Caucasian males), 51.8 (African-American males), 13.0 (Caucasian females), and 42.9 (African-American females) per 100,000 persons (JNC-VI, 1997). Hypertension is also correlated among family members and appears to be a polygenic and multifactorial disorder (Lander & Schork, 1994). Although the genetic relationship is not completely understood, genes controlling HTN probably affect one of the following three systems – renin-angiotensin-aldosterone, kallikrein-kinin, and/or sympathetic nervous system. Age is an undisputed contributing factor to HTN, with the prevalence of HTN rising with age. The most recent edition of the National Health and Nutrition Examination Survey (NHANES III, 1997) revealed that BP is significantly elevated among all Americans aged 60 and over (regardless of race and gender). Controllable risk factors refer to lifestyle habits and are potentially easier to modify than their uncontrollable counterparts. Lifestyle risk factors include obesity (body mass index greater than 27.0), diets high in sodium,

heavy and routine use of alcohol and/or tobacco, lack of exercise, and increased stress (JNC-VI, 1997).

Lastly, patients with co-existing health conditions are at greater risk for developing HTN. Nearly 40% of all patients with HTN have low-density lipoprotein cholesterol levels that meet the criteria for treatment with one of the statins, suggesting patients should also be on cholesterol-lowering therapy (Borghi et al., 2001). Individuals who have suffered from cerebral infarctions or cardiac failure, as well as those with coronary artery disease, left ventricular hypertrophy, and/or peripheral arterial disease are all predisposed to developing HTN (Kannel, 1990; Kaplan, 2001). In addition, the chances of developing HTN (or worsening HTN in patients previously suffering from it) are greater in patients diagnosed with renal diseases (renal parenchymal disease, renovascular disease), diabetes mellitus, dyslipidemia, and chronic obstructive pulmonary disorder.

II.2.c Pathophysiology, diagnosis, and clinical presentation

High BP is often due to arterial narrowing, which increases the pressure of blood flowing through these arteries and forces the arteries to work harder. Furthermore, patients with high BP are more likely to develop an enlarged heart, as high BP leads to an "overworked" heart and cardiac muscle atrophy. Changes in vessels leaving the heart and supplying the kidneys and brain may also affect these organs. The increased pressure on arteries may result in end-stage renal disease, cerebral infarction, or heart attack. Because the heart, brain and kidneys can handle increased pressure for a long time, patients with HTN are often asymptomatic and unaware that they have the condition.

Diagnosing HTN is based on routine BP monitoring and repeated detection of elevated BP. JNC has recommended a standard technique to measure BP and routine self-monitoring by patients for an accurate diagnosis. Once a hypertensive patient has been identified using this technique, additional laboratory tests and other diagnostic procedures may be warranted to help determine the cause of HTN (if there is one), the presence of other risk factors, or possible organ damage due to HTN. In instances of severe HTN, symptoms accompanying HTN (i.e., headache, palpitations, pallor, and perspiration) may be present and even suggest underlying conditions (i.e., renal or other cardiovascular disease).

II.2.d Patient management patterns

Treatment plans usually incorporate lifestyle/behavior modification with pharmacotherapy. According to the JNC-VI (1997), initial attempts to control HTN should focus on lifestyle/behavior modification (i.e., losing weight, reducing alcohol and tobacco intake, increasing physical activities, improving dietary habits). Several classes of anti-hypertensive pharmacotherapy (Table 2) are available and can be used alone or in combination with other drugs. Controlling HTN depends on the type of HTN (primary vs. secondary) and also the patient. For individuals who must be treated with pharmacotherapy, the presence of other co-morbid conditions, their tolerance of side effects, and the likelihood of their taking medications as prescribed must be considered when selecting appropriate agents.

Different treatment strategies are appropriate for different risk groups, depending on patients' co-morbidities and other risk factors for developing cardiovascular complications. Patients are broken down into three risk groups and treated accordingly: 1) HTN with no cardiovascular risk factors or co-morbidities (treat with lifestyle modification); 2) HTN with at least one cardiovascular risk factor but no co-morbidities (treat with lifestyle modification for 6-12 months before adding pharmacotherapy); and 3) HTN with at least one co-morbidity (treat with lifestyle modification and pharmacotherapy). Dose adjustments should be made at one or two-month intervals if the initial dose proves ineffective; at least two adjustments should be attempted before patients are switched to another drug or a second drug is added. The optimal formulation of a drug should provide 24-hour efficacy with a once-daily dose, which encourages better patient compliance and more consistent BP control.

Table 2. Selected oral anti-hypertensive agents in the US

Drug class and examples	Mechanism of action	Selected side effects
β-blockers	• Affect body's response to certain nerve impulses, decreasing force and rate of heart's contractions and lowering BP	Bradycardia, bronchospasm, heart failure, insomnia, fatigue, decreased exercise tolerance, impaired peripheral circulation, decreased sexual ability
α-blockers	• Control nerve impulses along certain nerve pathways, enabling blood vessels to relax and lowering BP	Dizziness, fatigue, headache , nervousness, irritability, stuffy or runny nose, nausea, pain in the arms and legs, general weakness
Angiotensin converting enzyme (ACE) inhibitors	• Prevent angiotensin I from being converted into a substance that increases salt and water retention in the body. • Induce relaxation of blood vessels	Dry persistent cough, headache, loss of taste, unusual tiredness, and nausea or diarrhea
Calcium channel blockers	• Slow movement of calcium into cells of blood vessels, relaxing blood vessels and lowering BP	Dizziness, flushing, headache, nausea, bradycardia
Angiotensin II receptor blockers	• Act at a later step in the same process of ACE inhibitors • Similarly lower BP by relaxing blood vessels	Nausea, headache, fatigue, diarrhea, dyspepsia, nasal congestion, limited angioedema, rare abnormal liver function
Vasodilators	• Relax muscles in blood vessel walls	Headache, nausea/vomiting, diarrhea, loss of appetite, joint/muscle pain, bradycardia
Diuretics	• Eliminate excess salt and water from body	Appetite, nausea and vomiting , stomach cramps, diarrhea and dizziness

Source: JNC-VI Guidelines, 1997
www.ahealthyme.com

II.2.e Place of product in therapy

Telmisartan is indicated for the treatment of HTN and may be used alone or in combination with other antihypertensive agents. In head to head studies with other angiotensin receptor blockers

(e.g. losartan and valsartan), telmisartan has shown similar or superior BP control. Additionally, telmisartan has been shown to provide consistent 24-hour BP control with once daily dosing. This characteristic is particularly important given the natural rise in BP in the early morning hours and the associated increase in cardiovascular events.

The American Diabetes Association guidelines support angiotensin receptor blockers as a preferred first line therapy for the treatment of nephropathy in hypertensive type 2 diabetics.

IIIA. CLINICAL EFFICACY SUPPORT FOR MICARDIS

This section of the dossier provides a review of the clinical evidence for telmisartan in the treatment of HTN alone or in combination with other anti-hypertensive agents. In general, telmisartan has been shown to be effective in the management of HTN when compared to placebo. It is equally effective or superior to enalapril (5-20 mg), atenolol (50-100 mg), amlodipine (5-10 mg), lisinopril (10-40 mg), losartan (50 mg) and valsartan (80 mg). Unless otherwise indicated, BP measurements were taken in each study with a sphygmomanometer while patients were in the supine position; in a few studies assessments were based on 24-hour ambulatory BP monitoring (ABPM). Additionally, all studies took into account trough assessments for BP to evaluate the efficacy of telmisartan over a 24-hour period with once-daily dosing.

This section is organized as follows:

- Sections III.1 – III.5 summarize information from clinical trials comparing telmisartan to placebo or active comparator, including other angiotensin-II receptor blockers, ACE-inhibitors, calcium-channel blockers, and □-blockers.
- Section III.6 discusses the efficacy of combination therapy of telmisartan and hydrochlorothiazide.
- Section III.7 examines the efficacy of telmisartan in controlling BP over a 24-hour period with once-daily dosing.
- Section III.8 explores off-label use of telmisartan as a cardiovascular protective agent.
- Section III.9 reviews the safety profile of telmisartan.
- Section III.10 includes summary tables of efficacy and safety for telmisartan.

III.1 Telmisartan vs. placebo (dose-ranging)

A dose-ranging study looked at different doses of telmisartan versus placebo. In one study, five doses of telmisartan (20-160 mg) were compared to placebo over a four-week period (Neutel & Smith, 1998). At study end, reductions in supine DBP ranged from 6.9 to 10.5 mmHg, while reductions in supine SBP ranged from 3.3 to 11.7 mmHg. In addition, a significant ($p<0.05$) dose-response relationship was seen for all doses up to the 80 mg dose.

III.2 Telmisartan vs. other angiotensin-II receptor blockers

Two studies compared telmisartan and losartan with placebo (Mallion et al., 1999; Neutel et al., 2000), while Littlejohn et al. (2000) were interested in the efficacy of telmisartan and valsartan. Mallion et al. (1999) evaluated two doses of telmisartan (40 mg, 80 mg) and losartan (50 mg)

against placebo. They determined that all active treatments were significantly (p<0.05) more effective than placebo in reducing BP; the greatest reductions from baseline (15.9 mmHg in SBP and 8.4 mmHg DBP) were seen with telmisartan 80 mg. Neutel et al. (2000) compared telmisartan (80 mg) with combination therapy of losartan (50 mg) and hydrochlorothiazide (12.5 mg). Reductions in DBP as measured by ABPM were observed with both treatments (8.3 mmHg and 10.3 mmHg for telmisartan and combination therapy, respectively). Although between-group differences were not significant, telmisartan monotherapy was equally as effective as losartan combination therapy. Littlejohn et al. (2000) used ABPM to compare monotherapy with telmisartan (80 mg) versus valsartan (80 mg). During the last six hours of measurement and during the final twenty-four hour period (trough), telmisartan was significantly (p<0.01) more effective than valsartan, with DBP reductions of 7.5 mmHg (telmisartan) versus 5.2 mmHg (valsartan). Reduction in SBP for telmisartan (10.5 mmHg) and valsartan (8.7 mmHg) were comparable (p=0.14).

III.3 Telmisartan vs. ACE-inhibitors

III.3.a Enalapril

Four studies compared telmisartan to enalapril. In a pivotal trial, Smith et al. (1998) compared four doses of telmisartan (40-160 mg) to enalapril (20 mg) and placebo over a 12-week period. Treatment with telmisartan was effective across all doses. Telmisartan and enalapril were both associated with significant (p<0.05) reductions (vs. placebo) in supine SBP and DBP by study end. Reductions with telmisartan treatment ranged from 10.0 to 11.9 mmHg in SBP and 8.6 to 9.7 mmHg in DBP. Karlberg et al. (1999) compared initial doses of telmisartan (20 mg) to enalapril (5 mg) in a 26-week study. Doses of both medications were increased stepwise (telmisartan to 40, then 80 mg; enalapril to 10 mg, then 20 mg) until week 12 of the study for patients not controlled with initial doses. For patients who remained uncontrolled on increased doses, hydrochlorothiazide (12.5-25 mg) was added. Clinically significant reductions in BP from baseline were exhibited. Mean reductions were 12.8 mmHg in DBP and 22.1 mmHg in SBP for telmisartan patients. Those treated with enalapril showed reductions of 11.4 mmHg (DBP) and 20.1 mmHg (SBP). In a third study, Neutel et al. (1999b) designed a similar study to that of Karlberg et al. (1999). Patients were treated with initial doses of telmisartan (80 mg) and enalapril (20 mg), which were doubled to 160 mg (telmisartan) and 40 mg (enalapril) for patients not responding to initial doses. Hydrochlorothiazide (25 mg) and subsequently amlodipine (5 mg) were added to regimens for patients uncontrolled on monotherapy with either drug. At the end of the eight-week study period, 55.2% and 34.8% of telmisartan and enalapril patients, respectively, were controlled. No patient was controlled with enalapril alone, while hydrochlorothiazide was added to the majority of telmisartan patients, as well. In the fourth study patients were treated with telmisartan (40-120 mg), enalapril (20 mg), or placebo over a four-week period (Telmisartan study #502.202, data on file – BI, 2001). Blood pressure was measured at 12 hours and 24 hours post-dosing. Compared to placebo, all telmisartan doses and enalapril significantly (p<0.01) reduced BP. Mean reductions in DBP 24 hours post-dosing ranged from 7.9 to 9.8 mmHg for telmisartan, 9.6 mmHg for enalapril, and 1.5 mmHg for placebo. Reductions in SBP ranged from 10.0 to 15.5 mmHg for telmisartan and 10.2 mmHg for enalapril. Systolic BP increased by 3.5 mmHg for the placebo group. Response rates, defined as a trough DBP of $\leq$ 90 mmHg or a reduction from baseline of $\geq$ 10 mmHg in trough DBP, ranged

from 45% to 61% for the telmisartan patients at study end. Nearly 62% of patients treated with enalapril and 19% of patients treated with placebo responded.

III.3.b Lisinopril

Neutel et al. (1999a) looked at the efficacy of telmisartan (40-160 mg) and lisinopril (10-40 mg) in a long-term (52-week) study. Doses of telmisartan and lisinopril were initially 40 mg and 10 mg, respectively, but were titrated upward to 160 mg and 40 mg in uncontrolled patients. Hydrochlorothiazide (12.5 mg) was added following these increases if patients remained uncontrolled on monotherapy. The year-long study was divided into two phases: titration phase (first 4-12 weeks of the study where doses were modified until patients were controlled) and a maintenance phase (up to 48 weeks where patients were maintained on doses achieved in the titration phase). Significant reductions in both SBP and DBP were achieved at the end of the titration phase. These reductions increased slightly by the end of the maintenance phase: patients on telmisartan showed reductions of 17.7 mmHg (SBP) and 15.9 mmHg (DBP), and BP of patients treated with lisinopril was reduced by 18.6 mmHg (SBP) and 15.5 mmHg (DBP). Significant between-group differences were not observed at the end of the titration or maintenance phases.

III.4 Telmisartan vs. calcium-channel blockers

Lacourciere et al. (1998) compared the efficacy of telmisartan (40 mg) and amlodipine (5 mg). Drugs were increased to 120 mg (telmisartan) and 10 mg (amlodipine) if patients did not respond to initial doses. Compared with placebo, both active treatments significantly ($p<0.001$) reduced BP as measured by conventional clinic cuff assessments. The reductions in supine SBP were 16.5 mmHg (telmisartan), 17.4 mmHg (amlodipine), and 3.4 mmHg (placebo). Reductions in DBP were 11.6 mmHg (telmisartan and amlodipine) and 4.5 mmHg (placebo). A significant ($p<0.0001$) reduction was also observed when measurements based on the ABPM technique were evaluated; these results are discussed in detail in Section III.7, "24-hour BP control with telmisartan."

III.5 Telmisartan vs. β-blockers

A study was conducted to compare the efficacy and safety of telmisartan, atenolol, and placebo (Telmisartan study #502.207, data on file – Boehringer Ingelheim, 2001). Medications were given once daily, and patients were randomized to receive initial doses of telmisartan (either 40 or 80 mg) or atenolol (50 mg). Doses were increased stepwise (telmisartan from 40 to 80 mg and 80 to 120 mg; atenolol from 50 to 100 mg) until week 12 of the study (study end) for patients not controlled with initial doses. Primary efficacy was defined as the change in DBP from baseline. Compared to placebo, both telmisartan dosing regimens and atenolol significantly ($p<0.01$) reduced supine DBP and SBP compared to placebo. Mean reductions in supine SBP/DBP were 12.3/8.4 mmHg and 16.2/9.1 mmHg for patients on 40-80 mg and 80-120 mg telmisartan, respectively. Those treated with atenolol showed reductions of 12.7 mmHg (supine SBP) and 10.8 mmHg (supine DBP). Response rates (defined as < 90 mmHg in supine DBP) were 46% (both doses of telmisartan), 51% (atenolol), and 19% (placebo). Between-group differences between telmisartan and atenolol were not significant.

III.6 Combination therapy of telmisartan and hydrochlorothiazide

McGill et al. (2001) conducted a study to determine what combinations of telmisartan and hydrochlorothiazide provide greater efficacy than monotherapy with either anti-hypertensive agent. Patients with mild to moderate HTN were enrolled in one of 20 treatment groups and were treated with one of the following regimens: monotherapy with telmisartan (20-160 mg) or hydrochlorothiazide (6.25-25 mg); combination therapy using any combination of doses; or placebo. The main regimens of interest were telmisartan 40 mg/hydrochlorothiazide 12.5 mg and telmisartan 80 mg/ hydrochlorothiazide 12.5 mg. Primary efficacy was defined as the change in supine trough DBP from baseline to study end. Results suggest that telmisartan 80 mg/ hydrochlorothiazide 12.5 mg significantly (p<0.01) reduced SBP/DBP compared to the individual components. Additionally, telmisartan 40 mg/HCTZ 12.5 mg significantly (p<0.01) resulted in better efficacy than the individual components for reducing SBP but not DBP.

III.7 24-hour blood pressure control with telmisartan

Several studies have been completed to assess the 24-hour efficacy of telmisartan using ABPM. These studies have been discussed in prior sections (based on telmisartan's comparator in each clinical trial); however, they are summarized here with particular detail to the method of BP monitoring.

Mallion et al. (1999) used ABPM to determine that reductions from baseline were significant (p<0.05) at all time points for both doses of telmisartan (40 and 80 mg) vs. losartan (50 mg) and placebo. In this six week, randomized, double-blind, parallel-group study of 223 patients with mild to moderate HTN, the primary endpoint was the reduction from baseline in BP during the 18 to 24 hour post-dose period. By study end reductions ranged between 11.5 mmHg to 13.3 mmHg (SBP) and 7.4 to 8.4 mmHg (DBP) for the telmisartan 40 mg and 80mg groups, respectively, as measured by ABPM. Reductions for losartan and placebo were 8.0/4.9 mmHg (SBP/DBP) and 1.8/0.8 mmHg, respectively. Results indicated that the differences between both doses of MICARDIS as compared to placebo (MICARDIS 40 mg vs. placebo p≤ 0.0001/p≤ 0.0001 [systolic/diastolic]; MICARDIS 80 mg vs. placebo p≤ 0.0001/p≤ 0.0001) as well as both doses of MICARDIS compared to losartan were statistically significant (MICARDIS 40 mg vs. losartan p≤ 0.0228/p≤ 0.0280; MICARDIS 80 mg vs. losartan p≤ 0.0030/p≤ 0.0145). During the last six hours of the dosing interval, reductions for the losartan group were not significantly different than the placebo group.

Lacourciere et al. (1998) compared the effects of telmisartan to amlodipine and placebo as measured by ABPM. Patients were administered telmisartan 40 mg (n=73, increased as necessary to 80-120 mg), amlodipine 5 mg (n=78, increased to 10 mg if necessary) or placebo (n=81). ABPM was done at baseline and at the end of the 12 week treatment period. As measured by ABPM, both telmisartan and amlodipine significantly reduced 24 hour mean SBP and DBP compared to placebo (p<0.0001) throughout the 24 hours dosing interval. Telmisartan resulted in significantly greater reductions in DBP as compared to amlodipine (p<0.05) during the night interval (2200-0600) and the last four hours of the dosing period. The 24 hour mean

DBP as measured by ABPM was <85 mmHg in 71% of the telmisartan treated patients and 55% of amlodipine treated patients (p=0.098).

Littlejohn et al. (2000) used ABPM to compare telmisartan 80 mg with valsartan 80 mg throughout a 24 hour dosing interval. Final BP at study end with telmisartan was 139.0/85.2 mmHg, compared with 142.8/88.6 mmHg for valsartan. Reductions in SBP and DBP were significant (p<0.01) in favor of telmisartan vs. valsartan. This was a prospective, randomized, open-label, blinded end point study which involved 35 centers in the United States. The main objective of the study was to compare the effectiveness of these two products in lowering BP over the last six hours of the dosing interval.

Four hundred twenty six patients with mild-to-moderate HTN entered the study; 393 patients (92%) completed the study. Following a four-week, placebo run-in period, patients were randomized to one of two treatment groups: MICARDIS 80 mg once daily (n=214) or valsartan 80 mg once daily (n=212) for an eight week treatment period.

Treatment with MICARDIS as compared to valsartan, resulted in a significantly greater reduction from baseline in mean DBP during the last six hours of the dosing interval as assessed by ABPM (-7.5 ± 0.6 mmHg vs. -5.2 ± 0.6 mmHg, respectively; p<0.01). There was no significant differences between treatment groups with respect to mean changes from baseline of SBP during the last six hours of the dosing interval (-10.5 ± 0.9 mmHg vs –8.7±0.9 mmHg, respectively; p=0.14). Likewise, mean 24 hour ABPM and seated trough cuff measurements of SBP and DBP at baseline did not differ significantly between the MICARDIS and valsartan treatment groups. Secondary analysis showed significantly greater efficacy with MICARDIS as compared to valsartan including larger mean reductions from baseline in SBP and DBP as measured by ABPM during the day (0600-2159) and larger decreases in trough cuff BP (p<0.01). Both treatments had adverse event profiles similar to placebo.

Lastly, Neutel et al. (2000) showed that telmisartan was at least equally effective as combination therapy of losartan and hydrochlorothiazide in reducing BP when measured using ABPM over a 24-hour period. The primary objective of this prospective, randomized, open-label, blinded-endpoint, parallel-group, study was to show that telmisartan 80 mg is as effective as the fixed dose combination of losartan 50 mg/HCTZ 12.5 mg in patients with mild-to-moderate HTN. The study included a four-week placebo run-in period and a six-week active treatment period with either telmisartan 80 mg (n = 332) or losartan 50 mg/HCTZ 12.5 mg (n = 350) once daily. In the intent-to-treat population, 24-hour ABPM DBP (mean +/- SD) decreased by 8.3 +/- 6.7 mmHg (from 93.2 +/- 6.7 mmHg to 84.9 +/- 8.1 mmHg) with telmisartan 80 mg and by 10.3 +/- 6.3 mmHg (from 93.8 +/- 6.6 mmHg to 83.4 +/- 8.1 mmHg) with losartan 50 mg/HCTZ 12.5 mg. The mean difference in DBP change between the groups, adjusted for baseline values and country, was -1.9 mmHg. The CI excluded a treatment difference of 3.0 mmHg or more. Consistent results were found in the analyses of secondary endpoints. Analysis of morning ABPM DBP means (06:00 - 11:59) and of trough cuff DBP confirmed the non-inferiority of telmisartan 80 mg versus losartan 50 mg/HCTZ 12.5 mg by ruling out a difference of 3 mmHg with 95 % confidence. This study showed that telmisartan 80 mg was as effective as a fixed dose combination of losartan 50 mg/HCTZ 12.5 mg with regard to the reduction in 24-hour mean ABPM DBP in patients with mild-to-moderate HTN. Both treatments provided BP control

during the early morning period, when patients are most likely to experience a cardiovascular event.

Reductions in BP based on ABPM for monotherapy with the three angiotensin II receptor blockers are summarized below in Table 3.

Table 3. Reductions in BP (mmgHg) based on ABPM

Parameter	Telmisartan	Valsartan	Losartan
Reduction in SBP (mmHg)	10.5* (p<0.01 vs. valsartan) 11.5† (telmisartan 40 mg) (p<0.05 vs. losartan) 13.3† (telmisartan 80 mg) (p<0.05 vs. losartan)	8.7*	8.0†
Reduction in DBP (mmHg)	7.5* (p<0.01 vs. valsartan) 7.4† (telmisartan 40 mg) (p<0.05 vs. losartan) 8.4† (telmisartan 80 mg) (p<0.05 vs. losartan)	5.2*	4.9†
Final BP at study end (mmHg)	139.0/85.2* 140.0/86.6† (telmisartan 40 mg) 147.9/85.3†(telmisartan 80 mg)	142.8/88.6*	140.0/86.3†

* Littlejohn et al., 2000
† Mallion et al., 1999

III.8 Off-label use of telmisartan

Although telmisartan is indicated for the treatment of HTN, several additional, off-label uses of the medication are under investigation. Initial studies of telmisartan therapy in patients with congestive heart failure (CHF) have been completed recently. Additional studies evaluating the use of telmisartan in patients with diabetes are in progress.

III.8.a Telmisartan use in patients with congestive heart failure

Therapy with ACE-inhibitors has been shown to reduce the morbidity and mortality associated with CHF. ACE-inhibitors probably achieve this phenomenon through a decrease in angiotensin II production and prevention of bradykinin breakdown. This mechanism suggests telmisartan may be even more effective in CHF patients, as telmisartan blocks the angiotensin II receptor without increasing bradykinin levels. One study conducted in Canada examined the neurohormonal (i.e., norepinephrine, plasma renin, angiotensin II) and hemodynamic (i.e., heart rate, mean arterial BP) effects of telmisartan in patients with CHF (Parker et al., 1999). Compared with placebo, a single dose of telmisartan (20, 40 and 80 mg) led to significant (p<0.05) decreases in mean arterial pressure at 8, 16, and 20 hours. Reductions observed in pulmonary capillary wedge pressure were significant for 40 and 80 mg. A dose-response relationship was observed for this parameter, as a linear trend was observed at 2 and 16 hours post-dose. Lower doses of telmisartan (10-20 mg) did not cause significant changes in angiotensin II levels, although this result was not maintained with higher doses (40-80 mg). In conclusion, a dose-dependent reduction in systemic arterial blood and pulmonary pressures was

seen, however, further studies are necessary to determine the impact of this finding in the clinical setting.

Dunselman (2001) studied the relationship between four doses of telmisartan (10, 20, 40 and 80 mg) and exercise capacity in patients with CHF. Patients were either treated with telmisartan or continued on enalapril 10 mg twice daily. The primary efficacy endpoint was defined as the change from baseline at study end in bicycle exercise duration. Additional efficacy endpoints included left ventricular ejection fraction, quality-of-life parameters, arterial BPs, neurohormonal changes and NYHA classification. Exercise duration increased by 1.4 seconds in patients treated with enalapril. Telmisartan led to increases ranging from 2.2 to 8.6 seconds, which were not significantly different from the enalapril duration. Furthermore, a dose-response relationship for telmisartan was not seen. Compared with enalapril, telmisartan (10 mg) led to a small but significant (p=0.001) increase in aldosterone levels. The drug also had a consistent and significant dose-dependent effect on angiotensin II levels.

III.8.b Telmisartan use in patients with diabetes

Essential HTN and subsequent renal failure are important concerns in patients with diabetes mellitus. ACE-inhibitors are known to exert a renal protective effect in diabetic, hypertensive patients. It is possible that angiotensin II receptor blockers may act similarly to ACE-inhibitors in these patients. To that end, a study is underway that compares the renal and anti-hypertensive effects of telmisartan and enalapril in diabetic patients with mild to moderate HTN. The study is designed to assess the renal consequences associated with each drug. Approximately 270 patients will be randomized to receive either telmisartan (40 mg) or enalapril (10 mg) over a 5-year period.

Additionally, Boehringer Ingelheim Pharmaceuticals, Inc. has plans to conduct two further Phase IV studies in diabetic patients. The first will evaluate the reduction of proteinuria in this patient population; the second is being conducted to evaluate BP control in the diabetic/obese population.

III.8.c Combination therapy to reduce cardiovascular morbidity and mortality

A trial comparing telmisartan monotherapy, ramipril (an ACE-inhibitor) monotherapy, and a combination of both drugs is being conducted to determine each therapy's efficacy in reducing cardiovascular morbidity and mortality. The endpoints of interest are the reductions in risk for cardiovascular mortality, stroke, myocardial infraction, and hospitalization for CHF. Patients will be treated with telmisartan (80 mg), ramipril (10 mg), or combination therapy (80 mg telmisartan/10 mg ramipril) and will be treated for five years.

ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) is a multi-center, double-blind, global trial that will assess the efficacy of ARB telmisartan alone and in combination with the angiotensin converting enzyme inhibitor ramipril, in preventing cardiovascular morbidity and mortality. The composite endpoints will be the reduction in risk of cardiovascular mortality, stroke, myocardial infarction and hospitalization for CHF. Patients will be randomized to three treatment arms. One group will receive ramipril 10

mg/day, initiating with a 5 mg dose and escalating, another group will receive telmisartan 80 mg/day, initiating with a 40 mg dose and escalating, and the third group will receive a combination of telmisartan 80 mg/day and ramipril 10 mg/day. Inclusion criteria include; patients ≥ 55 years old with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes mellitus *plus* at least one other CV risk factor such as: HTN, increased total cholesterol, low HDL cholesterol, smoking or documented microalbuminuria. Exclusions include patients with an ejection fraction of less than 0.40 or evidence of heart failure. Approximately 9,200 patients per group (28,000 total) will be recruited within two years and enrollment will begin in the second half of 2001. Patients will be observed for a maximum of five years. Up to three interim analyses are planned by the Data Safety Monitoring Board but these results will not be available since ONTARGET is a double-blind study. Patients or clinicians interested in more information on ONTARGET may visit the following website: www.ontarget-micardis.com.

III.9 Drug interactions-digoxin

The effects of MICARDIS on the pharmacokinetics of digoxin were studied in order to assess the potential for interaction between these two agents. This cross-over, randomized, open label study was conducted using telmisartan and oral digoxin in 12 healthy male volunteers (Stangier J et al. 2000).

No evidence of digoxin toxicity was observed in this population of young, healthy subjects. The combination of MICARDIS and digoxin was associated with a similar type, intensity and incidence of adverse events when compared to digoxin alone. Digoxin trough levels during monotherapy ranged from 0.328 to 0.575 ng/ml; during concurrent treatment with MICARDIS, trough levels ranged from 0.305 to 0.695 ng/ml. All of these concentrations of digoxin are generally lower than those observed in patients considered to be therapeutically digitalized (0.8-2.0 ng/ml).

The MICARDIS package insert states "*when telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentrations (49%) and in trough concentration (20%) were observed*." This statement is correct, however these numbers may overstate the magnitude and severity of the pharmacokinetic interaction that was actually observed in the study. It is critical to note that these percentages represent digoxin levels which were obtained closely following the oral administration of digoxin and therefore represent pre-distribution levels (e.g. peak digoxin levels were evaluated within two hours of administering digoxin on day 6 [144 hours]).

These investigators concluded that while changes in the pharmacokinetics of digoxin were observed, the resulting increases in peak digoxin concentrations and AUC with concomitant telmisartan therapy may not be clinically significant. *The risk of cardiac toxicity with digoxin is related only to steady-state and not peak concentrations. Therefore, based on the lack of significant differences in mean C_{min} observed, the authors concluded that adjustment of digoxin dose does not seem mandatory.* Note however, that this study was performed in normal healthy volunteers and that values may be altered in a population of patients with congestive heart failure.

The study design included two seven-day study periods separated by a 14-day washout period. During the first study period (treatment A, days 1-7), subjects were administered a 0.5 mg oral loading dose of digoxin on the morning of day 1, followed by 0.25 mg orally that evening. Participants were then administered 0.25 mg of oral digoxin once daily in the morning for the next six days (days 2-7). Treatment A also consisted of concomitant telmisartan 120 mg (standard doses of telmisartan [40 mg and 80 mg] were not studied) administered orally with each morning digoxin dose. Following the washout period (days 8-21), treatment B (days 22-28) consisted of the identical digoxin dosage regimen without concomitant telmisartan therapy. Plasma blood samples were obtained prior to the morning doses on days 1, 5, 6 of each study period. Additionally, a series of blood samples were drawn just before and 1, 2, 4, 6, 12 and 24 hours after drug administration on the seventh day of therapy during each period. Pharmacokinetic parameters for digoxin and telmisartan were calculated based on plasma concentrations determined by the blood samples obtained.

The primary study endpoints for determining if an interaction occurred were several pharmacokinetic parameters including area-under-the-concentration-time-curve ($AUC_{144-168}$), maximum concentration (C_{max}) and minimum concentration (C_{min}) of digoxin. Secondary endpoints evaluated included time to maximum concentration (T_{max}) and $C_{max}/AUC_{144-168}$ for digoxin as well as the pharmacokinetic parameters of telmisartan ($AUC_{144-168}$, C_{max}, C_{min} and T_{max}). Safety and tolerability of both agents were assessed by routine laboratory analysis, electrocardiogram and physician assessment.

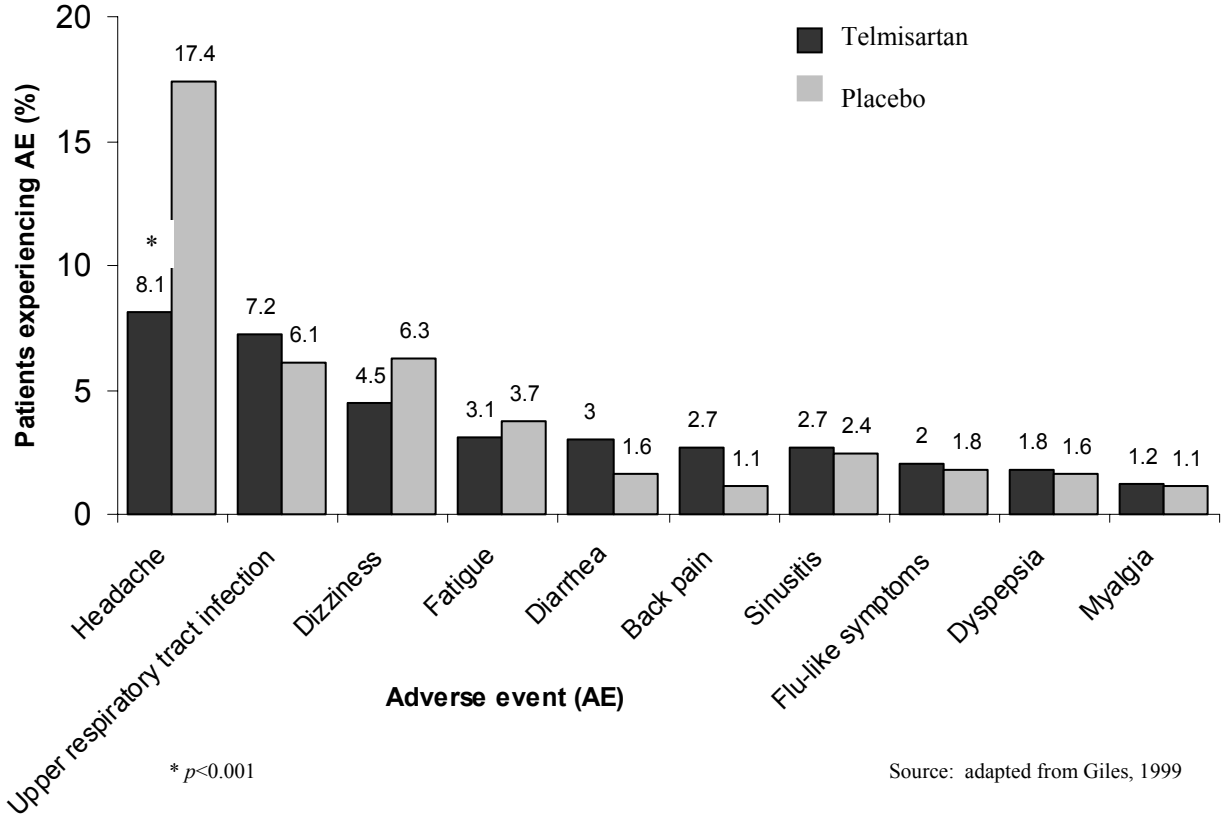
Mean serum digoxin concentration-time profiles determined in the study are shown in Figure 1. Results determined the 90% confidence interval (CI) for the primary endpoints of $AUC_{144-168}$ and C_{max} to be outside the designated limits, demonstrating a pharmacokinetic interaction. It was noted however that the differences in mean $AUC_{144-168}$ and C_{max} were most pronounced during the first four hours, suggesting this was the result of telmisartan increasing the rate of digoxin absorption (see Figure 1). The secondary endpoint of T_{max} was reduced and $C_{max}/AUC_{144-168}$ (a measure of the rate of absorption) was increased, also supporting this theory on the mechanism for the pharmacokinetic interaction. Conversely, the 90% CI for C_{min} was within limits suggesting a lack of pharmacokinetic drug interaction. The absolute difference between the trough concentrations was very small (ranging from 5 to 15%) and considered not clinically relevant. Also, it should be noted that the known half-life of digoxin in healthy adults ranges from 38-48 hours. Given the fact that it takes three to five half-lives for a drug to achieve steady-state plasma concentrations, it is possible that all subjects in the study did not achieve steady-state by the start of day seven.

As per the MICARDIS package insert, Boehringer Ingelheim Pharmaceuticals, Inc. recommends that digoxin levels be monitored when initiating, adjusting and discontinuing telmisartan to avoid possible over- or under- digitalization. Typically, digoxin levels are monitored once steady state has been achieved (e.g. approximately seven days following any change to a therapeutic regimen which could affect digoxin levels).

III.10 Safety of telmisartan

Adverse events associated with telmisartan are mild and transient, while overall tolerability of telmisartan is comparable to placebo. In general, the proportion of patients discontinuing treatment because of adverse events was less with telmisartan (2.8%) than with placebo (6.1%) (data on file – Boehringer Ingelheim). With the exception of headaches, whose incidence is significantly (p<0.001) higher in patients treated with placebo (17.4%) than with telmisartan (8.1%), the rates of adverse events are similar between telmisartan and placebo. These rates are depicted graphically in Figure 1.

Figure 1 Safety profile of telmisartan vs. placebo

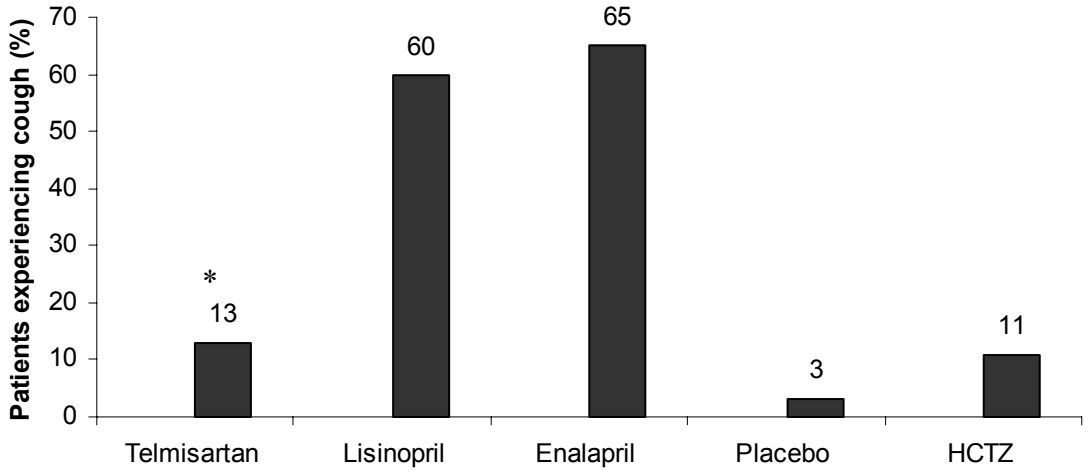


were documented; however, the frequency of these changes were comparable to frequencies observed in placebo patients (data on file – Boehringer Ingelheim, 2002).

Dry cough commonly occurs in patients treated with ACE-inhibitors (i.e., enalapril and lisinopril). Two short-term studies have shown the incidence of cough to be significantly lower in patients treated with telmisartan (Ramsay & Kirwan, 1998; Lacourciere et al., 1999). These studies are summarized in Table 5. Ramsay & Kirwan (1998) observed that the incidence of cough was significantly ($p\leq$0.001) higher in patients treated with enalapril (65%) vs. telmisartan (20%) or HCTZ (26%). Lacourciere et al. (1999) presented similar findings for another ACE-

inhibitor, lisinopril. Cough incidence was significantly (p<0.003) higher for lisinopril (60%) than for telmisartan (15.6%) and placebo (9.7%) based on the symptom assessment questionnaire (measuring incidence of positive cough response) and the visual analog scale (measuring frequency of cough). These findings are shown in Figure 2.

Figure 2 Incidence of cough in hypertensive patients



* $p \leq 0.001$ compared with ACE-inhibitor

Source: adapted from Ramsay & Kirwan, 1998; Lacourciere et al., 1999

III.11 Tabular summaries of clinical efficacy and safety

Tables 4-6 are summaries of relevant efficacy and safety trials for telmisartan. The following definitions are valid for all included studies:

- Primary efficacy variable – change from baseline in supine BP (systolic and diastolic)
- Diastolic response rate – reduction in supine DBP from baseline of $\geq$ 10 mm Hg
- Systolic response rate – reduction in supine SBP from baseline of $\geq$ 10 mm Hg
- Safety measured by occurrence of adverse events (AE), lab values, heart rate, and ECG

The following abbreviations are used in the tables:

ABPM	Ambulatory blood pressure monitoring
AML	Amlodipine
ATN	Atenolol
BP	Blood pressure
ENL	Enalapril
DBP	Diastolic blood pressure
HCTZ	Hydrochlorothiazide
HTN	Hypertension
LOS	Losartan
LSN	Lisinopril
SBP	Systolic blood pressure
TMS	Telmisartan
VAS	Valsartan

Table 4. Summary of efficacy of telmisartan

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Telmisartan vs. placebo (dose-ranging)			

Neutel & Smith, 1998	**Objective**
	• To assess dose-response relationship and safety of five doses of TMS in patients with mild to moderate HTN
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Randomized, double-blind, placebo-controlled, double-dummy
	• Phase III, principal trial
	
	Drug administration
	• 20-160 mg QD (TMS)
	• placebo QD
	
	Study period
	• 4-week run-in phase + 4-week double blind phase
		Study sample
		• N=274
		  • N=47 (TMS 20 mg)
		  • N=47 (TMS 40 mg)
		  • N=44 (TMS 80 mg)
		  • N=45 (TMS 120 mg)
		  • N=45 (TMS 160 mg)
		• 31% female
		• 18 ≤age ≥ 65
		
		Inclusion criteria
		• Mild to moderate HTN (DBP 100 mm Hg ≤ BP ≤ 114 mm Hg)
		
		Exclusion criteria
		• Secondary HTN
		• Cardiovascular, hepatic, renal disease
		• Diabetes mellitus
		• Heavy smokers (> 15 cigarettes)
		• Use of chronic concomitant therapy, diuretics, or other investigational drug therapy
			Primary efficacy
			• Primary efficacy defined as change from baseline in supine BP at trough (based on cuff assessment)
			• All TMS doses lowered trough BP significantly vs. placebo at study end ($p<0.0001$)
			  • Reduction in DBP ranged from 6.9 mm Hg to 10.5 mm Hg (greatest reduction → TMS 80 mg)
			  • Reduction in SBP ranged from 3.3 mm Hg to 11.7 mm Hg (greatest reduction → TMS 160 mg)
			• Decrease in BP initially seen after 1 week of treatment
			• Significant dose-response relationship observed
			
			Secondary efficacy
			• Secondary efficacy defined as trough supine DBP (≤ 90 mm Hg) and response rates for DBP and SBP
			• Diastolic response rate → all TMS doses significantly better than placebo ($p<0.05$)
			• Systolic response rate → TMS doses ≥ 40 mg significantly better than placebo ($p<0.05$)
			
			Safety
			• No significant differences in incidence of AEs between TMS and placebo groups
			• Most common AEs were:
			  • Dizziness → 1.8% TMS vs. 0% placebo
			  • Headache → 1.3% TMS vs. 2.2% placebo

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Telmisartan vs. other angiotensin-II receptor blockers			

Littlejohn et al., 2000	**Objective**
	• To determine efficacy and safety of TMS vs. VAS in patients with mild to moderate HTN
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Prospective, randomized, open-label, parallel group
	
	Drug administration
	• TMS 80 mg
	• VAS 80 mg
	
	Study period
	• 8 weeks (excluding run-in and washout periods)
		Study sample
		• N = 396
		  • N=199 (TMS)
		  • N=197 (VAS)
		• 68% male
		• age ≥ 18 years
		
		Inclusion criteria
		• mild to moderate HTN
		  • 95 mmHg ≤ DBP ≤ 114 mmHg
		  • 140 mmHg ≤ SBP ≤ 200 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Poorly controlled diabetes
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in SBP and DBP during last 6 hours of final 24 hour dosing interval (based on ABPM)
			• Reduction in DBP during last six hours of the dosing interval for TMS (7.5 mmHg) vs. VAS (5.2 mmHg) ($p<0.14$)
			• Significant reduction in SBP for TMS (10.5 mmHg) vs. VAS (8.7 mmHg) ($p<0.01$)
			• BP at study end based on ABPM → 139.0/85.2 TMS vs. 142.8/88.6 VAS ($p<0.01$)
			• BP at study end based on cuff measurement → 143.6/91.4 mmHg TMS vs. 147.6/94.1 mmHg VAS($p<0.01$)
			• Reduction in pulse rate → ≤ 0.6 beats/min for both groups (no significant differences between groups)
			
			Safety
			• No significant differences observed between treatment groups in frequency of AEs
			• Headache → 10.3% (TMS) vs. 10.4% (VAS) patients
			• Upper respiratory infection → 7.0% (TMS) vs. 6.1% (VAS) patients
			• No significant differences in lab parameters or ECG readings

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Mallion et al., 1999	**Objective**
	• To compare efficacy and tolerability of TMS vs. LOS in patients with mild to moderate HTN
	
	Setting
	• Multicenter
	• Multinational
	
	Design
	• Double-blind, parallel group, randomized study
	• Phase III, principal trial
	
	Drug administration
	• TMS 40 mg
	• TMS 80 mg
	• LOS 50 mg
	• Placebo
	
	Study period
	• 6 weeks (excluding run-in and washout periods)
		Study sample
		• N =207
		  • N=52 (TMS 40 mg)
		  • N=52 (TMS 80 mg)
		  • N=50 (LOS 50 mg)
		  • N=53 (Placebo)
		• 67% male
		• age ≥ 18 years
		
		Inclusion criteria
		• mild to moderate HTN
		  • 95 mmHg ≤ DBP ≤ 114 mmHg
		  • 140 mmHg ≤ SBP ≤ 200 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Poorly controlled diabetes
		• Chronic use of salt substitutes, oral anti-coagulants, NSAIDs, acetaminophen
		• Use of investigational drug known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in supine SBP and DBP at trough at study end (based on ABPM)
			• Significant reductions from baseline in BP for TMS 80 mg versus LOS and placebo and for 40 mg vs. LOS and placebo at all time points ($p<0.05$) for ABPM:
			  • TMS 40 mg → 11.5 mmHg (SBP), 7.4 mmHg (DBP)
			  • TMS 80 mg → 13.3 mmHg (SBP), 8.4 mmHg (DBP)
			  • LOS → 8.0 mmHg (SBP), 4.9 mmHg (DBP)
			  • Placebo → 1.8 mmHg (SBP), 0.8 mmHg (DBP)
			• Significant reductions from baseline in BP for TMS 40 mg and 80 mg vs. LOS and placebo at all time points ($p<0.05$) for cuff measurements (at clinic):
			  • TMS 40 mg → 14.2 mmHg (SBP), 8.6 mmHg (DBP)
			  • TMS 80 mg → 15.9 mmHg (SBP), 9.7 mmHg (DBP)
			  • LOS → 10.3 mmHg (SBP), 6.0 mmHg (DBP)
			  • Placebo → 4.8 mmHg (SBP), 3.5 mmHg (DBP)
			• Significantly more patients treated with TMS and LOS achieved normalization of BP at study end (32.7% TMS 40 mg; 46.2% TMS 80 mg; 28% LOS; 7.5% placebo)
			
			Safety
			• Frequency of AEs similar among all treatment groups
			• Headache, upper respiratory infection, dizziness, fatigue, pain most common AEs
			• Specific details not reported

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Neutel et al., 2000 (abstract)	**Objective**
	• To determine efficacy and safety of TMS vs. combination therapy of LOS + HCTZ
	
	Setting
	• Multicenter
	• Conducted in Europe and South Africa
	
	Design
	• Randomized, open-label, double-blind, parallel group
	
	Drug administration
	• TMS 80 mg
	• LOS 50 mg + HCTZ 12.5 mg
	
	Study period
	• 6 weeks (excluding washout and run-in periods)
		Study sample
		• N = 682
		  • N=332 (TMS)
		  • N=350 (LOS+HCTZ)
		• % male not specified
		• age not specified
		
		Inclusion criteria
		• not specified in abstract
		
		Exclusion criteria
		• not specified in abstract
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in DBP at trough at study end (as measured by ABPM)
			• Reduction in DBP by ABPM from baseline to study end → 8.3 mmHg (TMS), 10.3 mmHg (LOS+HCTZ)
			• Between-group difference not significant
			
			Safety
			• No significant difference observed between treatment groups in frequency of AEs
			• Details not provided in abstract

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Telmisartan vs. ACE-inhibitors			

Karlberg et al., 1999	**Objective**
	• To determine efficacy and safety of TMS vs. ENL in older patients with mild to moderate HTN
	
	Setting
	• Multicenter
	• Conducted in 3 Scandinavian countries
	
	Design
	• Double-blind, parallel group, randomized study
	
	Drug administration
	• TMS 20 mg (increased to 40 or 80 mg if needed until week 12)
	• ENL 5 mg (increased to 10 or 20 mg if needed until week 12)
	• HCTZ added to above if necessary after 12 weeks
	
	Study period
	• 26 weeks (excluding run-in and washout periods)
		Study sample
		• N = 278
		  • N=139 (TMS)
		  • N=139 (ENL)
		• 42% male
		• age ≥ 65 years
		
		Inclusion criteria
		• Mild to moderate HTN (supine DBP 95 mm Hg ≤ BP ≤ 114 mm Hg)
		• DBP could not vary by more than 10 mm Hg during placebo run-in period
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Poorly controlled diabetes
		• Chronic use of salt substitutes, oral anti-coagulants, NSAIDs, acetaminophen
		• Use of investigational drug known to affect BP
		• Supine SBP ≥ 220 mm Hg
		• Supine DBP ≥ 114 mm Hg
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in supine systolic and DBP at trough (based on cuff assessment)
			• Clinically significant reductions from baseline for both treatments:
			  • Supine DBP → 12.8 mmHg (TMS) and 11.4 mmHg (ENL) (p=0.074)
			  • Supine SBP → 22.1 mmHg (TMS) and 20.1 mmHg (ENL) (p=0.350)
			• 63% TMS patients and 62% ENL patients achieved target supine DBP of < 90 mmHg
			• 70% TMS patients and 67% ENL patients achieved a supine SBP of ≥ 10 mmHg
			• Reduction in pulse rate → 1.9 beats/min (TMS) and 2.4 beats/min (ENL)
			• 12 mg HCTZ added to patients not reaching target BP on monotherapy
			• A subgroup analysis (n=167) using ABPM showed both TMS and ENL produced significant reductions in SBP and DBP which were maintained throughout the 24 hour dosing interval
			
			Safety
			• No significant differences observed between treatment groups in frequency of AEs
			• Coughing → 6.5% (TMS) vs. 16% (ENL) patients
			• Vertigo → 0.7% (TMS) vs. 3.6% (ENL) patients
			• Diarrhea → 4.3% (TMS) vs. 2.2% (ENL) patients
			
			Quality of life
			• No changes between baseline and study end in any domain of SF-36 (quality of life instrument with 8 domains)

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Neutel et al., 1999a	**Objective**
	• To determine efficacy and safety of TMS vs. LSN
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Prospective, randomized, double-blind, parallel group
	
	Drug administration
	• TMS 40 mg (up to 80 or 160 mg if needed)
	• LSN 10 mg (up to 20 or 40 mg if needed)
	• Open-label HCTZ (12.5 mg or 25 mg) added if BP remained uncontrolled after TMS or LSN doses increased
	
	Study period
	• 1 year (excluding washout and run-in periods) broken into titration period (TP) and maintenance period (MP)
	  • TP (4-12 weeks) → dosing altered until adequate BP control reached
	  • MP (48 weeks) → patients maintained on adequate dose
		Study sample
		• N = 448
		  • N=303 (TMS)
		  • N=145 (LSN)
		• 65.5% male
		• age ≥ 18 years
		
		Inclusion criteria
		• mild to moderate essential HTN → 95 mmHg ≤ DBP ≤ 114 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in trough supine BP at study end (based on cuff assessment)
			• Significant reduction in SBP and DBP for both TMS and LSN from baseline at end of titration period
			  • Reduction in SBP for TMS (13.9 mmHg) and LSN (12.4 mmHg)
			  • Reduction in DBP for TMS (11.8 mmHg) and LSN (10.9 mmHg)
			• % of patients achieving BP control at end of titration period:
			  • 36% (TMS 40 mg), additional 15% (TMS 80 mg), and additional 16% (TMS 160 mg)
			  • 32% (LSN 10 mg), additional 17% (LSN 20 mg), and additional 15% (TMS 40 mg)
			• Significant reduction in SBP and DBP for TMS and LSN from baseline at end of maintenance period
			  • Significant reduction in SBP for TMS (17.7 mmHg) and LSN (18.6 mmHg)
			  • Significant reduction in DBP for TMS (15.9 mmHg) and LSN (15.5 mmHg)
			• End of maintenance period → 44% TMS vs. 48% LSN patients completed phase without HCTZ
			• Significant reduction in SBP and DBP for patients treated with HCTZ at end of maintenance period
			  • Significant reduction in SBP for TMS (23.8 mmHg) and LSN (19.9 mmHg)
			  • Significant reduction in DBP for TMS (16.6 mmHg) and LSN (15.6 mmHg)
			
			Safety
			• Significant difference observed between treatment groups in frequency of AEs; 28% TMS vs. 40% LSN (p=0.001)
			• Headache → 5% (TMS), 6% (LSN)
			• Cough → 3% (TMS), 7% (LSN)
			• No significant differences in lab parameters or ECG readings

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Neutel et al., 1999b	**Objective**
	• To determine efficacy and safety of TMS vs. ENL in patients with severe HTN
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Open-label study
	
	Drug administration
	• TMS 80 mg (up to 160 mg if needed)
	• ENL 20 mg (up to 40 mg if needed)
	• Open-label HCTZ 25 mg + AML 5 mg if BP remained uncontrolled after TMS or LSN doses increased
	
	Study period
	• 8 weeks (excluding washout and run-in periods)
		Study sample
		• N = 73
		  • N=49 (TMS)
		  • N=24 (ENL)
		• 75.5% male
		• age ≥ 18 years
		
		Inclusion criteria
		• Severe HTN → 115 mmHg ≤ DBP ≤ 130 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in supine BP at trough at study end (based on cuff assessment)
			• Supine SBP/DBP: 14.6/13.2 TMS and 13.0/12.9 ENL
			• % of patients achieving BP control (DBP <90 mmHg):
			  • On initial dose → 3.6% (TMS), 0% (ENL)
			  • On increased dose → 7.5% (TMS), 0% (ENL)
			  • Active treatment + HCTZ → 33.9% (TMS), 20.8% (ENL)
			  • Active treatment + HCTZ + AML → 55.2% (TMS), 34.8% (ENL)
			• % of patients achieving response at study end (DBP < 90 mmHg, or reduction in DBP ≥10 mmHg) → 91% (TMS), 93% (ENL)
			
			Safety
			• No significant difference observed between treatment groups in frequency of AEs
			• Headache → 19% (TMS), 25% (ENL)
			• Upper respiratory tract infection → 9% (TMS), 21% (ENL)
			• Cough → 0% (TMS), 7% (ENL)
			• No significant differences in lab parameters or ECG readings

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Study #502.202 (data on file - Boehringer Ingelheim)	**Objective**
	• To determine efficacy and safety of TMS vs. ENL
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Prospective, randomized, open-label, parallel group
	• Phase II
	
	Drug administration
	• TMS 40 or 80 mg once daily (increased to 80 or 120 mg if needed)
	• ENL (20 mg) once daily
	• Placebo
	
	Study period
	• 4 weeks (excluding run-in period)
		Study sample
		• N = 207
		  • N=40 (TMS 40 mg)
		  • N=41 (TMS 80 mg)
		  • N=41 (TMS 120 mg)
		  • N=42 (ENL 20 mg)
		  • N=52 (placebo)
		• 62% male
		• age ≥ 18 years
		
		Inclusion criteria
		• mild to moderate HTN
		  • 95 mmHg ≤ DBP ≤ 114 mmHg
		  • 140 mmHg ≤ SBP ≤ 200 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Poorly controlled diabetes
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in trough supine DBP at study end
			• Reduction in supine DBP from baseline significant vs. placebo
			  • TMS 40 mg → 7.9 mmHg (p<0.001)
			  • TMS 80 mg → 8.7 mmHg (p<0.001)
			  • TMS 120 mg → 9.8 mmHg (p<0.0001)
			  • ENL → 9.6 mmHg (p<0.0001)
			  • Placebo → 1.5 mmHg
			• Reduction in supine SBP from baseline significant vs. placebo (p<0.0001)
			  • TMS 40 mg → 10.0 mmHg (p<0.0001)
			  • TMS 80 mg → 15.5 mmHg (p<0.0001)
			  • TMS 120 mg → 12.5 mmHg (p<0.0001)
			  • ENL → 10.2 mmHg (p<0.0001)
			  • Placebo → increase of 3.5 mmHg
			• % of patients achieving BP control at study end:
			  • TMS 40 mg → 45%
			  • TMS 80 mg → 51%
			  • TMS 120 mg → 61%
			  • ENL → 62%
			  • Placebo → 19%
			
			Safety
			• Two serious cardiovascular events (myocardial infarction and markedly elevated BP) observed in TMS patients (no relationship between event and TMS established)

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Smith et al., 1998	**Objective**
	• To determine efficacy and safety of TMS vs. ENL
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Prospective, randomized, open-label, parallel group
	• Phase III, principal
	
	Drug administration
	• TMS 40, 80, 120, 160 mg
	• ENL 20 mg
	• Placebo
	
	Study period
	• 12 weeks (excluding run-in and washout periods)
		Study sample
		• N = 440
		  • N=72 (TMS 40 mg)
		  • N=72 (TMS 80 mg)
		  • N=73 (TMS 120 mg)
		  • N=75 (TMS 160 mg)
		  • N=72 (ENL)
		  • N=76 (placebo)
		• 42% male
		• age ≥ 18 years
		
		Inclusion criteria
		• Mild to moderate HTN
		  • 95 mmHg ≤ DBP ≤ 114 mmHg
		
		Exclusion criteria
		• Hepatic, renal, cardiovascular dysfunction
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in supine systolic and DBP at trough at study end (based on cuff assessment)
			• Reduction in supine BP → 11.6/9.3 mmHg (TMS 40 mg), 11.8/9.7 mmHg (TMS 80 mg), 10.0/8.8 mmHg (TMS 120 mg), 11.9/8.6 mmHg (TMS 160 mg), 8.2/7.2 mmHg (ENL)
			• Significant reduction in SBP for all doses of TMS and ENL vs. placebo
			• No significant differences seen between men and women; white patients had better response than black patients
			
			Safety
			• Incidence of treatment-emergent AEs between treatment groups similar
			• Lower incidence of treatment-related AEs in TMS groups but not significant
			• Cough → 0.3% (TMS) vs. 4.2% (ENL) patients vs. 1.3% (placebo)
			• Headache → 2.1% (TMS) vs. 2.8% (ENL) patients vs. 1.3% (placebo)
			• No significant differences in lab parameters or ECG readings
			• No significant differences observed between treatment groups in pulse rates

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Telmisartan vs. calcium-channel blockers			

Lacourciere et al., 1998	**Objective**
	• To determine efficacy, duration of action and safety of TMS vs. AML in patients with mild to moderate HTN
	
	Setting
	• Multicenter
	• Conducted in Canada
	
	Design
	• Prospective, randomized, double-blind, parallel group
	• Phase III, principal trial
	
	Drug administration
	• TMS 40 mg (increased to 80 or 120 mg if needed until week 12)
	• AML 5 mg (increased to 10 mg if needed until week 12)
	• Placebo
	
	Study period
	• 12 weeks (excluding run-in and washout periods)
		Study sample
		• N = 232
		  • N=73 (TMS)
		  • N=78 (AML)
		  • N=81 (placebo)
		• 65% male
		• age ≥ 28 years
		
		Inclusion criteria
		• Mild to moderate essential HTN → 95 mmHg ≤ DBP ≤ 114 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in supine DBP and SBP at trough at study end (based on cuff assessment)
			• Secondary efficacy measurements also based on ABPM
			• Cuff BP measurements detected no difference between AML and TMS
			• Significant reduction in supine and standing BP for TMS and AML vs. placebo ($p<0.0001$)
			  • Significant reduction in supine SBP for TMS (16.5 mmHg) and AML (17.4 mmHg)
			  • Significant reduction in supine DBP for TMS (11.6 mmHg) and AML (11.6 mmHg)
			• Increase in drug dose for TMS ($p<0.01$) and AML ($p<0.05$) led to further reduction in BP vs. placebo
			• Discontinuation of TMS or AML not associated with rebound HTN
			• Significant reductions observed with ABPM for TMS and AML vs. placebo across all time points of dosing intervals ($p<0.0001$)
			
			Safety
			• Edema → 5% (TMS), 22% (AML), 6% (placebo); significantly more common in AML patients vs. TMS ($p=0.001$) and placebo ($p=0.03$)
			• Headache → 17.8% (TMS), 29.6% (placebo), 20.5% (AML)
			• No significant differences in lab parameters or ECG readings
			• No significant change in heart rate in any study group

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Telmisartan vs. β-blockers			

Study #502.207 (data on file - Boehringer Ingelheim)	**Objective**
	• To determine efficacy and safety of TMS vs. ATN
	
	Setting
	• Multicenter
	• Conducted in Europe
	
	Design
	• Prospective, randomized, open-label, parallel group
	• Phase III
	
	Drug administration
	• TMS 40 or 80 mg once daily (increased to 80 or 120 mg if needed)
	• ATN 50 mg once daily (increased to 100 mg if needed)
	• Placebo
	
	Study period
	• 8 weeks (excluding run-in period)
		Study sample
		• N = 229
		  • N=117 (TMS 40-120 mg)
		  • N=59 (ATN 50-100 mg)
		  • N=52 (placebo)
		• 67% male
		• age ≥ 18 years
		
		Inclusion criteria
		• mild to moderate HTN
		  • 95 mmHg ≤ DBP ≤ 114 mmHg
		  • 140 mmHg ≤ SBP ≤ 200 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Poorly controlled diabetes
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in trough supine DBP at study end
			• Reduction in supine DBP from baseline significant vs. placebo
			  • TMS 40 mg → 8.4 mmHg (p<0.001)
			  • TMS 80 mg → 9.1 mmHg (p<0.0001)
			  • ATN 50 mg → 10.8 mmHg (p<0.0001)
			• Reduction in supine SBP from baseline significant vs. placebo
			  • TMS 40 mg → 12.3 mmHg (p<0.01)
			  • TMS 80 mg → 16.2 mmHg (p<0.0001)
			  • ATN 50 mg → 12.7 mmHg (p<0.01)
			• Response pattern for standing BP similar to supine BP (TMS 80 mg showed largest numerical reduction)
			
			Safety
			• Incidence of treatment-emergent AEs between treatment groups similar
			• Headache and dizziness most commonly reported AEs
			• No significant differences in lab parameters or ECG readings
			• No significant differences observed between TMS and placebo in pulse rates (ATN significantly lowered pulse rate compared with placebo and TMS)

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Combination therapy with HCTZ			

McGill & Reilly, 2001	**Objective**
	• To determine efficacy of different combinations of TMS+HCTZ compared to monotherapy
	
	Setting
	• Multicenter
	• Conducted in US
	
	Design
	• Prospective, randomized, double-blind, parallel group, placebo-controlled
	
	Drug administration
	• TMS 20-160 mg
	• HCTZ 6.25-25 mg
	• 12 combination therapies of TMS+HCTZ (focus: TMS 40/HCTZ 12.5 mg; TMS 80/HCTZ 12.5 mg)
	• Placebo
	
	Study period
	• 8 weeks (excluding run-in period)
		Study sample
		• N = 818
		  • N=209 (TMS)
		  • N=121 (HCTZ)
		  • N=414 (TMS+HCTZ)
		  • N=74 (placebo)
		• 60% male
		• age ≥ 18 years
		
		Inclusion criteria
		• Mild to moderate HTN (SBP: 114-200 mmHg; DBP: 95-114 mmHg
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Chronic use of drugs known to affect BP
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as change from baseline in trough supine DBP at study end
			• Significant (p<0.01) reduction in supine SBP and DBP for TMS 80/HCTZ 12.5 mg vs. TMS or HCTZ monotherapy
			  • TMS 40 mg/HCTZ 12.5 mg → 18.8/12.6 mmHg (p<0.01)
			  • TMS 80 mg/HCTZ 12.5 mg → 23.9/14.9 mmHg (p<0.01)
			  • TMS 40 mg → 12.2/10.7 mmHg
			  • TMS 80 mg → 15.4/11.5 mmHg
			  • HCTZ 12.5 mg → 6.9/7.3 mmHg
			  • Placebo → 2.9/3.8 mmHg
			• % of patients achieving BP control at study end (defined as response in SBP or DBP):
			  • TMS 40 mg/HCTZ 12.5 mg → 81% (SBP), 63% (DBP)
			  • TMS 80 mg/HCTZ 12.5 mg → 85% (SBP), 79% (DBP)
			  • TMS 40 mg → 60% (SBP), 67% (DBP)
			  • TMS 80 mg → 66% (SBP), 69% (DBP)
			  • HCTZ 12.5 mg → 36% (SBP), 47% (DBP)
			  • Placebo → 29% (SBP), 29% (DBP)
			• TMS 80 mg/HCTZ 12.5 mg significantly (p<0.01) better efficacy than individual components in reducing SBP or DBP
			• TMS 40 mg/HCTZ 12.5 mg significantly (p<0.01) better efficacy than individual components in reducing SBP but not DBP
			
			Safety
			• No significant difference observed between active treatment groups in frequency of AEs
			• No significant differences in pulse rates observed between all treatment groups
			• Upper respiratory infection → 7.2% (TMS), 9.9% (HCTZ), 8.0% (TMS/HCTZ), 6.8% (placebo)
			• Headache → 7.2% (TMS), 9.1% (HCTZ), 4.1% (TMS/HCTZ), 16.2% (placebo)
			• Dizziness → 3.8% (TMS), 5.8% (HCTZ), 5.1% (TMS/HCTZ), 1.4% (placebo)
			• No significant differences in lab parameters or ECG readings

Table 5. Summary of off-label use of telmisartan

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Parker et al., 1999	**Objective**
	• To determine hemodynamic and neurohormonal effects of telmisartan vs. placebo in patients with congestive heart failure
	
	Setting
	• Multicenter
	• Conducted in Canada
	
	Design
	• Prospective, randomized, parallel group, double-blind, placebo-controlled
	
	Drug administration
	• TMS 10-80 mg
	
	Study period
	• Study measurements taken over 24-hour period
		Study sample
		• N = 81
		  • N=16 (TMS 10 mg)
		  • N=16 (TMS 20 mg)
		  • N=16 (TMS 40 mg)
		  • N=17 (TMS 80 mg)
		  • N=16 (placebo)
		• 91% male
		• 18 ≤ age ≤ 80 years
		
		Inclusion criteria
		• Mild to moderate congestive heart failure (NYHA class II, III)
		• LVEF ≤ 35%
		
		Exclusion criteria
		• Clinically significant valvular disease
		• Mechanical heart valve
		• Hyptertrophic or restrictive cardiomyopathy
		• Atrial flutter
		• SBP < 90 mmHg
		• Acute ischemic syndrome
		• Episode of syncope or cardiac arrest
		• Intracoronary intervention or major surgery within past 3 months
		• Hepatic or renal dysfunction
		• Prior treatment with or known hypersensitivity to telmisartan
		• Pregnant women or those of child-bearing potential
			Primary hemodynamic endpoint
			• Primary hemodynamic endpoint defined as change from baseline to peak response in hemodynamic parameter (mean arterial pressure)
			• Significant (p<0.05) reduction in mean arterial pressure seen for 20, 40, 80 mg TMS (peak effect observed at 8, 8, 16 hours post-dose, respectively)
			• Significant (p<0.05) reduction in pulmonary capillary wedge pressure seen for 40, 80 mg TMS (peak effect observed at 2 and 16 hours post-dose, respectively); dose-response relationship documented
			• No significant effect on heart rate, right atrial pressure, cardiac index, or peripheral vascular resistance
			
			Secondary hemodynamic endpoint
			• Secondary hemodynamic endpoint defined as change from baseline in SBP and DBP at study end
			• Significant reductions observed with all TMS doses in SBP; significant reduction seen with 20 mg for DBP
			• Significant dose-response trend in mean arterial BP observed over 12-hour period
			
			Neurohormonal effects
			• Significant (p<0.05) increase in plasma renin at 6 hours for 20 mg TMS; significant increase at all post-dose times for 40, 80 mg TMS
			• No effect on plasma norepinephrine
			• No significant change in angiotensin II levels for 10, 20 mg TMS
			• Significantly (p<0.05) elevated angiotensin II levels for 40 mg (3, 6, 24 hours post-dose) and 80 mg (3 hours post-dose)
			
			Safety
			• Hypotension (1 patient → 80 mg TMS)
			• Hypovolemia (1 patient → placebo)
			• High filling pressure (2 patients → 40 mg TMS, placebo)

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Dunselman, 2001	**Objective**
	• To determine effects of maximal exercise tolerance of TMS vs. ENL in patients with congestive heart failure
	
	Setting
	• Multicenter
	• Conducted in Europe
	
	Design
	• Prospective, randomized, parallel group, double-blind
	
	Drug administration
	• TMS 10, 20, 40 and-80 mg
	• ENL 10 mg BID
	
	Study period
	• 12 weeks
		Study sample
		• N = 378
		  • N=301 (TMS)
		  • N=77 (ENL)
		• 89% male
		• 21 ≤ age ≤ 80 years
		
		Inclusion criteria
		• mild to moderate congestive heart failure (NYHA class II, III) and LVEF ≤ 40%
		
		Exclusion criteria
		• Clinically significant valvular disease
		• Hyptertrophic or restrictive cardiomyopathy
		• Major surgery within past 6 months
		• Hepatic or renal dysfunction
		• Prior treatment with or known hypersensitivity to telmisartan
		• Pregnant women or those of child-bearing potential
		• Any life-threatening disease
		• History of MI, unstable angina
		• Significant stenotic valvular disease
		• Patients requiring phosphodiesterase inhibitors, dopamine, beta agonists, class I antiarrhythmics or chronic NSAIDs
			Efficacy
			• Primary efficacy endpoint defined as increase in exercise duration from baseline
			• No significant difference observed between treatment groups (increase of 1.4 seconds for ENL and 2.2 to 8.6 seconds for TMS)
			• No difference in exercise capacity between doses of TMS
			• No significant differences observed for change in ejection fraction
			• Most patients (60% across all treatment groups) reported no change in functional capacity
			• No difference in SBP between groups
			• No difference in quality of life, based on Minnesota Living with Heart Failure questionnaire
			• Dose-response trend seen for neurohormones among TMS patients
			• TMS can replace ENL in patients with CHF without adversely affecting exercise capacity
			
			Safety
			• Incidence of AEs similar across treatment groups
			• Cough → 2.9% (TMS), 5.6% (ENL)

Table 6. Summary of safety of telmisartan

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Ramsay & Kirwan, 1998 (abstract)	**Objective**
	• To determine incidence of dry cough of TMS vs. ENL vs. HCTZ
	
	Setting
	• Multicenter
	• Conducted in Europe
	
	Design
	• Double-blind, parallel group, randomized, placebo-controlled
	
	Drug administration
	• TMS 80 mg
	• ENL 20 mg
	• HCTZ 25 mg
	
	Study period
	• 8 weeks
		Study sample
		• N = 119
		  • N=38 (TMS)
		  • N=37 (ENL)
		  • N=44 (HCTZ)
		• % male not identified
		• age not identified
		
		Inclusion criteria
		• ACE-inhibitor cough identified during single-week challenge phase
		
		Exclusion criteria
		• Not specified
			Efficacy
			• Primary efficacy defined as incidence of dry cough
			• Incidence of dry cough significantly higher for ENL (65%) vs. TMS (20%) and HCTZ (26%) ($p<0.001$ for TMS; $p=0.001$ for HCTZ)
			• Reduction in BP from baseline effective for TMS (16.8/10.6 mmHg), ENL (10.6/8.0 mmHg), and HCTZ (8.0/5.4 mmHg)
			• TMS not significantly associated with dry cough

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Lacourciere et al., 2000	**Objective**
	• To determine incidence of dry cough of TMS vs. LSN
	
	Setting
	• Multicenter
	• Conducted in Canada
	
	Design
	• Double-blind, parallel group, randomized, placebo-controlled
	
	Drug administration
	• TMS 80 mg
	• LSN 20 mg
	• placebo
	
	Study period
	• 8 weeks
		Study sample
		• N = 88
		  • N=32 (TMS)
		  • N=25 (LSN)
		  • N=31 (placebo)
		• 39% male
		• age > 18 years
		
		Inclusion criteria
		• History of ACE-inhibitor related dry cough
		
		Exclusion criteria
		• Known/suspected secondary HTN
		• Hepatic, renal, cardiovascular dysfunction
		• Upper respiratory infections or allergic rhinitis associated with cough
		• Poorly controlled diabetes
		• Chronic use of salt substitutes, oral anti-coagulants, NSAIDs, acetaminophen
		• Pregnant women or those of child-bearing potential
			Efficacy
			• Primary efficacy endpoint defined as incidence of dry cough
			• Incidence of dry cough significantly higher for LSN (60%) vs. TMS (15.6%) and placebo (9.7%) (p=0.001 for both groups vs. LSN)
			• Frequency of dry cough significantly higher for LSN vs. TMS and placebo (p=0.0028 vs. placebo; p=0.0016 vs. TMS)
			• Reduction in BP vs. placebo significant for TMS and LSN
			• Reductions from baseline → 9.3/8.3 mmHg TMS vs. 15.1/9.3 LSN
			
			Safety
			• AEs reported fro 53.1% TMS, 44.4% LSN, 66.7% placebo patients

IIIB. PHARMACOECONOMIC SUPPORT FOR TELMISARTAN

A pharmacoeconomic modeling study was conducted to estimate potential impact of telmisartan in the treatment of HTN (Richter et al., 2001). Specifically, the study examined differences in costs associated with telmisartan versus other anti-hypertensive agents including amlodipine, atenolol, enalapril, and hydrochlorothiazide (Table 6). The study evaluated costs associated with therapy (initial drug costs and maintenance therapy costs) and physician visits for patients who experienced adverse events, needed dose adjustments, or were switched to other therapies. The investigators collected data regarding treatment patterns and resource utilization for other anti-hypertensive agents through literature review and a Delphi panel. Telmisartan-specific data was gathered from clinical trials. Cost data for drugs and resource utilization were obtained from published secondary sources and standardized to a per-patient, per-quarter level. Outcomes of interest included the time to BP control (as this affects the number of physician visits, number of drug switches, number of dose adjustments) and the cost of treatment.

Patients initiating therapy with telmisartan had the fastest mean time to control at 2.73 months vs. 3.75 months for the slowest therapy, enalapril. Initiating therapy with telmisartan was also the second least expensive option with total costs of $2382 for 15 months (versus the two most expensive options of enalapril and amlodipine). Hydrochlorothiazide was the least expensive option but had the second slowest time to control. Sensitivity analyses revealed that telmisartan remains relatively inexpensive as efficacy varies between 40% and 80%. At 80% efficacy, only hydrochlorothiazide was cheaper than telmisartan but with a significantly longer time to control than telmisartan. At 40% efficacy, telmisartan took the longest to achieve BP control but remained one of the cheaper options. These results are summarized in below.

Therapy	Time to BP control (months)	Total cost (over 15-month period)
Telmisartan	2.73	$2392
Amlodipine	2.83	$3018
Atenolol	3.04	$2426
Enalapril	3.75	$2838
Hydrochlorothiazide	3.41	$2057
Overall *(using probabilities of initial therapy choice)*	3.25	$2452

Source: Richter et al., 2001

Table 7. Summary of pharmacoeconomic analyses of telmisartan

Citation	Study Design	Methods	Findings

Richter et al., 2001	**Objective**
	• To examine the differences in costs associated with TMS vs. other anti-hypertensive therapy (AML, ATN, ENL, HCTZ)
	
	Study type
	• Decision-analytic model to determine cost-effectiveness of telmisartan vs. "other" agents
	• Perspective – third-party payer
	
	Outcomes
	• Costs per quarter (drug cost per dose; maintenance costs for treatment of AEs)
	• Clinical efficacy (expected time to control BP)
		Inclusion criteria
		• Participated in clinical efficacy trials for TMS
		
		Costs inputs
		• Drug therapy
		• Treatment for AEs
		• Physician visits
		• Costs reported in 1997 US $
		
		Data sources
		• Data regarding treatment patterns and resource utilization for HTN (and adverse events associated with therapy) collected through literature review and Delphi panel (physician survey)
		• TMS-specific data collected from clinical trials to determine efficacy and adverse event rates
		• Cost data for drugs gathered from published sources (*RedBook*, 1997; physician fee schedule; inpatient hospitalization data)
		
		Analyses
		• Time to BP control (affects number of physician visits, number of drug switches, number of dose adjustments) measured for drugs
		• Sensitivity analyses
			Results
			• TMS showed fastest time to control (2.73 months vs. 3.75 months for ENL)
			• Initiating therapy with TMS is the second least expensive option → $2382 for 15 months
			• Treatment with HCTZ is least expensive → $2057 for 15 months (3.41 months to control)
			• Treatment with AML is most expensive → $3018 for 15 months (2.83 months to control)
			• TMS more costly in only three scenarios →
			  • when rate or cost of severe edema (AE) dropped by >70%
			  • individual analyses from two trials
			• When efficacy of TMS varied from 40% - 80%, it is equally effective as other therapies

IV. IMPACT MODEL REPORT

A spreadsheet model has been developed to allow a health plan to estimate the annual budgetary impact of adding telmisartan to a health plan's formulary. Based on this model, this section of the dossier presents a review of the findings from a budget impact analysis involving the addition of telmisartan to the formulary of a hypothetical health plan as well as the switch of a comparator drug to telmisartan.

IV.1 Model description

IV.1.a Purpose

The spreadsheet model is developed to allow a health plan to evaluate the budgetary impact of adding telmisartan to a health plan's formulary. Specifically, the model focuses on the comparison between the use of telmisartan and two comparators, losartan and valsartan. Models such as this one can aid decisions regarding the addition of a new product to the formulary, help define its specific role in the health plan's environment, and assist in creating benchmarks against which the product's future performance can be measured. The model is designed to be flexible, transparent, and easily used.

IV.1.b Model structure

The budget impact model was developed in Microsoft Excel® spreadsheet format. Health plan staff will be able to input plan-specific data. However, default values are provided for model calculations. The budget impact model reflects a prevalence framework as HTN is a chronic condition. The prevalence framework represents the patterns of treatment experienced by health plan members over a one-year period.

IV.1.c Subsections of the model

The budget impact model includes the following sections:

- Introduction
- Assumption
- Flow Chart
- Plan Epidemiology
- Drug Treatment Pattern
- Drug Share
- Clinical Parameters
- Resource Utilization

- Unit Costs
- Health Plan Budget Summary

Each section is described below. This section provides a full description of the model and how it is intended to be used.

Introduction, Assumption and Flow Chart
The model outcomes, the assumptions, and the episode of care are illustrated in these sheets.

Plan Epidemiology
In this section, the user is first asked to provide information on the health plan members, including size of enrollment and demographic characteristics such as age distribution and risk groups. Default values have been provided to allow the model calculations to run.
Next, in order to evaluate the budget impact of a new treatment for HTN, the prevalence of HTN in the health plan's population must first be determined. Default values for the prevalence of HTN have been provided based on well documented literature (Heart and Stroke Update 2001). The model assumes that all HTN patients seek medical care for their condition. This information will give the health plan a general idea of the impact of HTN on plan members' lives.

Drug Treatment Patterns
This section projects the proportion of health plan members with HTN prescribed angiotensin-II receptor blockers as a first-line therapy. The box at the top of this section first outlines the proportion of HTN patients who seek medical treatment, by level of severity – high normal, mild or moderate to severe. This model can be used to compare telmisartan to either valsartan or losartan. For purposes of simplicity, the user can choose which comparison is to be made throughout the model to best suit the plan characteristics. The user can also choose the market share of each drug with the user's own inputs in the drug share sheet.

Drug Share
When an initial drug dosage fails to provide the desired effect, physicians titrate the dose upward to the next available dose. To allow this titration, the user will be able to choose any available doses, 25mg, 50mg or 100mg for losartan and 80mg, 160mg or 320mg for valsartan. Similarly, users will be able to choose any dose available for telmisartan including 20mg, 40mg and 80mg. When patients take 80mg telmisartan and titration is needed, the next option is to combine 80mg telmisartan and HCT 12.5mg as a combination therapy.

Clinical Parameters
The response rates are obtained from two published papers summarizing the clinical trial results. Head to head comparison between telmisartan and losartan (valsartan) is evaluated for a 6 week (8 week) trial period. The values taken from these trials can be altered for a sensitivity analysis.

Resource Utilization
Default values have been provided for the average number of office visits made by patients once they enter one of the treatment pathways provided. Once again, these default values are based on literature. JNC-VI guideline indicates that most patients should be seen within 1 to 2 months after initiation of therapy to determine the adequacy of HTN control. Therefore, taking a

conservative approach in the model, patients initiating therapy are seen by the physician after being treated for 3 months. If the patient's HTN has been controlled on initial therapy, they will remain on therapy and be seen again in another 3 months. If a patient has uncontrolled HTN at the initial 3 month visit, they will be every month by the physician until their BP is controlled. However, the practice patterns within different health plans may vary greatly, and users are strongly encouraged to enter more appropriate data if available.

Unit Costs

A unit cost is identified for each separate resource item included in the budget impact model. In this section, the derivation and source for each unit cost figure is detailed in the text "comment" box linked to each cell.

Summary of Annual Costs

Total direct medical costs for the HTN population using telmisartan and a comparator within the health plan are summarized in the box labeled "Health plan budget summary." Based on this cost figure, the PMPM (per member per month) and the PTMPM (per treated member per month) figures are also calculated. The principal cost drivers in HTN treatment are medical encounters and prescription drugs. Annual costs for each group are calculated by assigning unit costs (defined in the section labeled "Unit cost list") to the resource utilization data from the "Resource utilization" section.

IV.2 Model Navigation

The user should navigate through the model one spreadsheet at a time, moving left to right across the labeled tabs at the bottom of the screen. For example, the user should select the "Plan Epidemiology" spreadsheet, enter any changes to the data, and then move to the next spreadsheet labeled "Drug Treatment Pattern," and so forth. On the "Plan Epidemiology," the user has the option of entering the name of the health plan. This may be useful if the user wants to print results from any modeling exercises.

Each spreadsheet provides buttons that allow the user to restore default values that have been provided and used for the baseline analysis. Some spreadsheet sections have more than one "Restore Defaults" button. Each button on those spreadsheets will restore the values for the column of data above the button. If the user wants to restore ALL model default values at one time, a "Restore All Defaults" button has been provided at the bottom of the "Health Plan Budget Summary" spreadsheet. If the user wants to print all the outcomes of the analysis after providing plan specific inputs, he or she may use the button, "Print All Sheets" provided next to the "Restore All Defaults" button.

The information entered into the "Plan epidemiology," "Drug share," "Clinical parameters," "Resource utilization," and "Unit cost" spreadsheets are used to calculate annual treatment costs and monthly per-patient costs that are shown at the top of the "Health plan budget summary" spreadsheet. The annual per-patient costs from the "Health plan budget summary" spreadsheet are combined with the number of patients following each treatment pathway (from the "Chart" spreadsheet) to calculate the total annual health plan costs, summarized at the top of the "Health plan budget summary" spreadsheet.

The user can move to the "Health plan budget summary" spreadsheet to estimate the budgetary impact of switching patients that are currently using either losartan or valsartan to telmisartan. In order to conduct this study, in the "Drug Share" spreadsheet, the user should specify the proportion of the patients with HTN in each severity category that will be switched to telmisartan. Based on all of the model inputs, the "cost saving due to switch" box in this spreadsheet provides a summary of the annual cost savings that may be incurred by a health plan if they switch some or all of their current patients using comparator drugs to telmisartan.

IV.3 Model Overview

The budget impact analysis was based on product specific budgetary impact. This means that the model does not address the annual cost of all currently available HTN treatments within the health plan, but it does address the annual cost of treating a cohort of patients using telmisartan as opposed to other comparators.

The model evaluates the budgetary impact of adding telmisartan to a health plan formulary, including an assumed switch from a comparator drug to telmisartan. The differential impact of telmisartan versus losartan or valsartan on health care utilization is determined by a one-year prospective economic evaluation of data from clinical trials in the treatment of HTN. This model can be used to compare telmisartan to either losartan or valsartan. The choice of the latter drugs was due to the readily available direct comparative data.

IV.4 Model Inputs (prevalence, clinical trials and optimizing patient care)

Model inputs and default numbers used for the analysis are described below.

In the "Plan epidemiology" section of the model, users can input the following information:

- Number of enrollees
- Age distribution
- Prevalence of HTN (estimated at 25 % for persons aged 18 and older)
- Distribution of each severity category (44.5 % high-normal risk group, 43.9 % mild risk group, 11.6 % moderate and severe risk group)

For the "Drug treatment pattern" component of the analysis, the following assumptions were included in the model for the hypothetical health plan:

- 10% of patients with HTN receive an angiotensin-II receptor blockers drug, while the rest of them receive one of the following drug regimens:
  - Diuretic Drug Class
  - Beta Blocker
  - CCB
  - ACE Inhibitor
- The model assumes that 100% of patients who use an angiotensin-II receptor blockers drug are currently using either telmisartan or one of the comparators such as losartan or valsartan, and that some or all of these patients would be switched to telmisartan.

- The user can change the drug doses administered by selecting the desired dose from the drop down menu contained in the cells with the white background. For telmisartan, the default doses are set at 40mg for patients with high-normal or mild HTN and 80mg for patients with moderate to severe HTN. For losartan, the defaults doses are 50mg for all different risk groups. For valsartan, 80mg is set as the default dose across patients with high normal, mild or moderate to severe HTN. The basic analysis is performed using these default numbers.

In the "Clinical parameter section" of the model, the response rates are illustrated.

- The response rate is defined as the proportion of patients achieving DBP level below 90mm Hg and/or a decrease in DBP of > 10 mm Hg.
- These clinical values are from the published clinical trials. The differences in response rates are based on two comparisons: 1) telmisartan 40mg and losartan 50mg for patients with mild to moderate HTN 2) telmisartan 80mg and valsartan 80mg for patients with mild to moderate HTN.

For the "Resource utilization section" of the model, a number of assumptions are made according to JNC-VI guideline.

- JNC-VI guideline indicates that most patients should be seen within 1 to 2 months after initiation of therapy to determine the adequacy of HTN control.
- Once BP is stabilized, follow-up at 3 to 6 month intervals is generally appropriate for office visits.
- For patients with uncontrolled BP, more frequent visits to physicians are assumed.

In the "Unit cost" section of the model:

- The AWP for a 30-day supply of telmisartan 40mg and 80mg was assumed at $42.15 and $45.06 respectively, whereas a 30-day supply of losartan 50 mg and valsartan 80mg is assumed at $45.44 and $41.93 respectively.
- Drugs considered as representative in each drug class are listed in the table and used for the analysis. The probabilities that these drugs are used in a combination therapy with angiotensin-II receptor blockers are drawn from the literature [Richter et al.(2001) "Mild to moderate uncomplicated HTN: further analysis of a cost-effectiveness study of five drugs." Manage Care Interface July P.61-69].The weighted average price is obtained by assigning probabilities to each drug

IV.5 Model Outcomes

IV.5.1 Annual cost of HTN treatment

- The "Plan epidemiology" component of the analysis indicated that 10% of the estimated 162,500 patients in the health plan receiving treatment for HTN were prescribed angiotensin-II receptor blockers during the one-year period. The model considered two scenarios.
- In one scenario, it was assumed that all of these patients were prescribed either telmisartan or losartan. The results of the analysis indicated that the total annual HTN-

specific costs for the patient using telmisartan were $17.7 million, which translated to $1.48 per member per month, and $9.09 per treated HTN patient per month. If all were taking losartan, the total annual HTN-specific costs for the patient using losartan were $21.2 million, which translated to $1.77 per member per month, and $10.87 per treated hypertensive patient per month. Also, it was estimated that patients using telmisartan would use 11.5% fewer physician visits than they would when losartan was prescribed.

- In a separate scenario, it was assumed that all of these patients were prescribed either telmisartan or valsartan. The total annual HTN-specific costs were $15.9 million for the patients using telmisartan and $17.2 million for patients using valsartan. In addition, it was estimated that patients using telmisartan compared to valsartan would incur 15.2% fewer costs for physician visits
- Consequently, the model indicates that those who were taking either losartan or valsartan incur 19.6% and 8.6 % greater total costs in HTN treatment than those using telmisartan.
- These savings are equivalent to $0.29 PMPM for losartan and $0.11 PMPM for valsartan

IV.5.2 Impact of drug switches

The model examined the budgetary impact of switching some or all of these 16,250 patients from comparators to telmisartan. The results of the analysis indicated the following:

- If 10% of 16,250 patients were switched from losartan (valsartan) to telmisartan, the health plan would save $347,248 ($137,548) in HTN-specific costs over a one-year period which translated into a 1.6% (0.8%) reduction in HTN specific costs over a one-year period.
- If 50% of 16,250 patients were switched from losartan (valsartan) to telmisartan, the health plan would save $1,736,238 ($687,739) in HTN-specific costs over a one-year period which translated into a 8.1% (4.0%) reduction in HTN specific costs over a one-year period.
- If all 16,250 patients were switched from losartan (valsartan) to telmisartan, the health plan would save $3,472,476 ($1,375,478) in HTN-specific costs over a one-year period.
- The total savings of about $3,579,696 ($1,375,478) represented a 16.3% (8.0%) reduction in the costs of treating this population for the health plan.
- The monotonic increase in the cost savings induced by the drug switches are depicted in the “Graph” section of the analysis.

V. CLINICAL VALUE AND OVERALL COST

The preceding sections of this dossier have presented the 1) clinical rationale to support the acceptance and use of telmisartan in the treatment of HTN, and 2) pharmacoeconomic evidence for telmisartan. These demonstrate the pharmacologic and economic value which telmisartan provides when chosen as treatment for HTN.

V.1 Clinical value of telmisartan

Telmisartan has displayed equivalent or superior efficacy compared to other drugs in its class, including angiotensin II receptor blockers, as well as traditional anti-hypertensive agents (i.e., calcium channel blockers, β-blockers, and ACE-inhibitors). The effect of telmisartan is summarized below:

- During the last six hours of a 24 hour dosing interval, telmisartan 40 mg and 80 mg were each significantly better than losartan 50 mg at reducing both SBP and DBP (Mallion 1999)
- During all monitored periods, telmisartan 80 mg significantly reduced SBP and DBP as compared to placebo and losartan; telmisartan 40 mg was superior to losartan for both SBP and DBP during the night time dosing interval and was as effective as losartan during the day and morning periods (Mallion 1999).
- Micardis (40 to 80 mg) treated patients experienced slightly greater reductions in both SBP and DBP as compared to amlodipine (5-10 mg) treated patients during the 24 hour dosing interval however, this difference did not reach statistical significance (Lacourciere 1998).
- Telmisartan 80 mg significantly reduced SBP and DBP as compared to valsartan 80 mg during the morning, day time and 24 hour dosing intervals. Telmisartan also significantly reduced DBP more than valsartan during the last six hours of the dosing interval. Telmisartan was equal but not superior to valsartan at reducing SBP and DBP during the night time interval and for SBP during the last six hours (Littlejohn 2000).
- Telmisartan 80 mg was as effective as losartan 50 mg/HCTZ 12.5 mg at reducing the 24 hour mean DBP as measured by ABPM, SBP results were not reported (Neutel 2000).
- Therapy with both lisinopril (10-40 mg) and telmisartan (40-160 mg) resulted in significant reductions from baseline in SBP and DBP at the end of a 48 week trial. The percent of patients achieving BP control at the end of the titration period of this trial was 67% and 63% for telmisartan and lisinopril treated patients, respectively (Neutel 1999a).
- The effect on SBP and DBP for both telmisartan (20-80 mg) and enalapril (5-20 mg) were similar and were significant when compared to baseline values. The response rates for attaining BP control for both enalapril and telmisartan were also comparable (Karlberg 1999).
- When the effect of telmisartan (80-160 mg)and enalapril alone, or in combination with HCTZ (25 mg) and amlodipine (5 mg) were compared for effect on DBP response after eight weeks of therapy, 91% of patients in the telmisartan arm and 93% of patients n the enalapril arm responded to therapy (Neutel 1999).
- Telmisartan 40, 80, 120 or 160 mg as well as enalapril 20 mg significantly ($p<0.05$) reduced both SBP and DBP when compared to placebo. Final reductions for all telmisartan doses ranged from 10.0-11.9/8.6-9.7 mmHg; final reductions with enalapril were 8.2/7.2. The antihypertensive effect of telmisartan was at least as effective as enalapril (Smith 1998).

- Telmisartan 80 mg/HCTZ 12.5 mg was significantly better at reducing both SBP and DBP when compared to the individual components. Telmisartan 40 mg/HCTZ 12.5 mg was significantly better at reducing SBP but not DBP when compared to the individual components (McGill 2001).
- It is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing telmisartan to avoid possible over- or under- digitalization. However, based on the lack of significant differences in mean C_{min} observed, an adjustment of digoxin dose does not seem mandatory.
- Telmisartan has a adverse event profile similar to placebo; the incidence of cough associated with telmisartan is significantly lower than was seen with enalapril or HCTZ (Ramsay 1998).
- In addition to its anti-hypertensive effects, telmisartan is currently being evaluated for unapproved indications including its effect on proteinuria in diabetic patients and its effect on congestive heart failure..
- Additionally, an outcome trial (ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) with 28,000 patients comparing telmisartan alone and in combination with ramipril is being conducted to compare their effects in preventing cardiovascular morbidity and mortality.

V.2 Safety profile of telmisartan

Telmisartan's safety profile is analogous to that of placebo, according to a recent analysis by Giles (1999). As discussed in Section III.9, 45.8% of individuals treated with telmisartan monotherapy reported at least one adverse event, compared with 46.6% of placebo patients. This safety profile is also what distinguishes telmisartan (and other angiotensin-II receptor blockers) from ACE-inhibitors. Many patients treated with ACE-inhibitors experience dry, nonproductive cough, whereas those treated with telmisartan do not. The minimal incidence of this and other adverse events result in a favorable safety profile for telmisartan. Better tolerability is expected to increase patient compliance, which leads to better BP control (Meredith, 1999).

V.3 Dosing regimen of telmisartan

Telmisartan's ability to maintain a reduction in BP over a 24-hour period with once-daily dosing is another desirable characteristic. Telmisartan has a mean half-life of 24 hours and has shown a sustained duration of effect. Several studies compared telmisartan to amlodipine, valsartan, or losartan (Littlejohn et al., 2000; Mallion et al., 1999; Neutel et al., 2000). Investigators used ABPM and reported that telmisartan significantly ($p<0.05$) reduced BP over a 24-hour period including the last six hours of the dosing interval. Maintaining consistent BP control over a 24-hour period is clinically beneficial. A rapid increase in BP has been correlated with neuroendocrine activities and may also result in myocardial infarction and sudden death (Deedwania & Nelson, 1990; Muller et al., 1985; Willich et al., 1987). Assessments with ABPM have shown that the greatest incidence of episodes of silent myocardial ischemia occur within the first two hours of individuals awakening (Neutel et al., 1999c). In the section of this document on ABPM, we have shown that telmisartan is able to control BP during these critical hours. Controlling the early morning BP rise is essential to minimize the risk of cardiovascular morbidity and mortality.

An additional benefit of long-acting hypertensive agents, such as telmisartan, is their positive impact on patient compliance. Compliance is highest with once-daily medications – whose duration of effect is sustained over a 24-hour period – as patients are more likely to remember taking drugs once a day than twice a day. Leenan et al. (1997) have shown that a long-acting anti-hypertensive agent provides greater control of BP than that achieved with shorter-acting agents.

V.4 Cost-effectiveness of telmisartan

The use of telmisartan leads to reduction in total costs in the management of hypertensive treatment. When compared to losartan and valsartan in our impact model, telmisartan produced short-term (e.g., 1 year) cost savings and may potentially produce long-term (e.g., lifetime) cost savings. Patients attaining a level of controlled BP require fewer follow-up visits to physicians and avoid both dose increases and combination therapy. Such a reduction in costs could have a significant budgetary impact for managed care plans.

1,000,000 enrollees and 162,500 hypertensive patients were set as default inputs. For telmisartan, the default doses are 40mg for patients with high-normal or mild HTN and 80mg for patients with moderate to severe HTN. Default doses for losartan are 50mg for all risk groups. 80 mg valsartan is standard across patients with all levels of HTN severity. Based on these inputs, the economic modeling indicates that the cost saving will be $3,472,476 when enrollees currently treated with losartan switch to telmisartan. Similarly, when these enrollees switch from valsartan, the cost saving will be $1,375,478. These figures translate into 16.3% or 8.0 % reduction in the total costs respectively. Due to the expected spillover effect of HTN treatment improving other cardiovascular diseases, annual cost savings should be greater in the future than the ones demonstrated in the model.

In summary, several features of telmisartan distinguish this drug and support its addition to a managed care plan's formulary. Besides showing equivalent efficacy as traditional anti-hypertensive agents, telmisartan has a safety profile similar to placebo. Additionally, the drug confers 24-hour BP control, which minimizes potentially harmful BP variability, and may also reduce costs associated cardiovascular morbidity and mortality often associated with poor HTN control.

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*Articles enclosed